Available online at www.annclinlabsci.org

Analysis of Cerebrospinal Fluid and Serum CEA Concentration in Non-neoplastic Diseases

Qiang Shi[1], Chenglin Tian[1], Xusheng Huang[2], and Chuanqiang Pu[2]

[1]Department of Neurology, Hainan Branch of Chinese PLA General Hospital and [2]Department of Neurology, Chinese PLA General Hospital, Beijing, China

Abstract. ***Background.*** Carcinoembryonic antigen (CEA) in cerebrospinal fluid (CSF) is important for the diagnosis of meningeal carcinomatosis. Its relationship with CSF and serum in non-neoplastic diseases may be beneficial for earlier diagnosis and treatment. ***Methods.*** CSF samples were obtained from 346 non-neoplastic inpatients. Among them, 238 pairs of CSF and serum were obtained and compared. The 97.5th percentile and maximum value of CSF CEA were obtained. ***Results.*** The 97.5th percentile and maximum value of CSF CEA concentration for overall participants were 0.529 and 2.340 μg/L, respectively. The ratio of CEA level (CSF/serum) was from 0.017 to 1. CSF CEA concentration was equal to the simultaneous serum concentration only in 0.84% (2/238) and no higher than simultaneous serum CEA concentration was found. ***Conclusion.*** The value determined in this study of CSF CEA is significantly lower than that usually used in clinical practice. CSF CEA concentration higher than the simultaneous serum CEA concentration suggests abnormal intrathecal CEA secretion.

Key words: Carcinoembryonic antigen, cerebrospinal fluid, serum, meningeal carcinomatosis.

Introduction

Meningeal carcinomatosis is an uncommon, usually late, complication of cancer with an average untreated survival from four to six weeks. Neuroimaging studies (computerized axial tomography, magnetic resonance, and isotope studies of cerebrospinal fluid flow) are necessary to evaluate associated metastases and detect obstruction of cerebrospinal fluid flow [1]. Positive cerebrospinal fluid cytological findings confirm the diagnosis. Because of the lack of sensitivity of this test (50%–60% at initial lumbar puncture, which can be improved to 80% with repeated sampling of CSF [2,3]), considerable efforts have been made to identify alternative diagnostic markers.

Evaluation of intrathecal tumor markers synthesis is a specific, sensitive, reliable, and reproducible diagnostic tool [4]. Carcinoembryonic antigen (CEA), a β-1 glycoprotein with a high molecular weight of 180 kDa, is produced in adenocarcinomas such as gastrointestinal cancer, breast cancer, lung cancer, ovarian cancer, and pancreatic cancer [5,6]. Approximately half (50-60%) of this protein is composed of hydrocarbons like sialic acid, mannose, galactose, acetyl-N-glucosamine, and fructose. The other 40% or so is composed of polypeptides. Small amounts of CEA exist in normal digestive organs and various bodily fluids such as urine, intestinal secretions, pleural fluid, peritoneal fluid, and cerebrospinal fluid [7-9]. Normal serum CEA level in our laboratory is defined as less than 5μg/L.

Neurological complications including brain metastasis and meningeal carcinomatosis seriously affect the quality of life in patients with advanced cancer, or even directly lead to death. CEA as a marker has been shown to be useful diagnostically in these pathologies [10-14].

Despite the fact that the measurement of CSF CEA is widely used for the diagnosis of brain metastasis and meningeal carcinomatosis, the upper reference limit of CSF CEA in people without central nervous system or systemic malignant tumours, which is the foundation for determining an abnormal elevation of CSF CEA, has not been fully elucidated. We will evaluate CSF CEA in this article.

Address correspondence to Chuanqiang Pu, Department of Neurology, Chinese PLA General Hospital, haidian district fuxing road 28, Beijing, 100853, China; fax: 86 010 66939251; e mail: shiq301@yeah.net

0091-7370/16/0200-180.

Table 1. *The CSF and serum CEA concentrations in overall, male and female participants in different age groups.*

Cohort	CSF CEA concentration (mg/L)					Serum CEA concentration (mg/L)				
	No.	Minimum	Median	97.5th percentile	Maximum	No.	Minimum	Median	97.5th percentile	Maximum
Overall	346	0.200	0.200	0.529	2.340	238	0.200	1.625	2.442	11.950
Gender										
Male	208	0.200	0.200	0.430	2.340	144	0.200	1.760	6.902	11.950
Female	138	0.200	0.200	0.592	1.920	94	0.310	1.510	5.680	11.290
	P value (Mann-Whitney U test)				0.467	*P* value (Mann-Whitney U test)				0.002
Age (years)										
<21	39	0.200	0.200	0.427	0.500	19	0.430	1.200	2.931	2.940
21-40	85	0.200	0.200	0.501	0.673	50	0.200	1.435	5.766	11.290
41-50	91	0.200	0.200	0.900	2.340	68	0.200	1.515	5.426	7.890
51-60	70	0.200	0.200	0.517	0.661	53	0.471	1.900	7.349	11.950
61-99	61	0.200	0.200	0.396	0.490	48	0.810	2.230	6.951	10.120
	P value (Kruskal-Wallis H test)				0.868	*P* value (Kruskal-Wallis H test)				<0.0001

Materials and Methods

Subjects. A total of 208 male and 138 female inpatients from the Department of Neurology were included in this study. Their mean age was 44.870±16.793 years, ranging from 5 to 99 years. At the time of discharge, the diagnoses of these patients mainly included central nervous system infection, inflammatory demyelinating disease, peripheral neuropathy, cerebral venous sinus thrombosis, systemic or primary central nervous system vasculitis and degenerative disease. Lumbar puncture was performed by the physicians in charge for clinical diagnostic purposes. All patients bore no evidence of central nervous system or systemic malignant tumours. This study has been reviewed and approved by the Ethic Committee of PLA General Hospital. Written consents were signed by all participants or their guardians.

Measurement of CSF and serum CEA. All samples were measured on Roche Modular Analytic E170 analyser (Roche company, Germany) including 238 pairs of CSF and serum samples and 108 separate CSF samples.

Statistical analysis. The CSF CEA concentration was given as a minimum, maximum and percentile. Gender and age differences in CSF CEA concentrations that had skewed distributions were tested with the Mann-Whitney U rank-sum test and Kruskal-Wallis H test, respectively. The CEA concentrations in each paired sample of CSF and serum from 238 subjects were compared. All statistical tests were performed with SPSS 16 (SPSS Inc, Chicago, Illinois). A statistically significant difference was considered as $p<0.05$.

Results

The minimum and maximum values of CSF CEA concentration were 0.2μg/L and 2.34 μg/L for all participants, 0.2μg/L, and 2.34μg/L for male participants and 0.2μg/L and 1.92μg/L for female participants. The 97.5th percentile of CSF CEA concentration was 0.529μg/L for all, 0.43μg/L for male, and 0.592μg/L for female participants **(Table1)**. The results of serum CEA concentrations were also summarised in **Table 1**. CSF CEA concentrations in female participants were not significantly different from male participants; however, the serum CEA concentrations in female participants were significantly different from male participants. There was no statistically significant age difference in CSF CEA concentration of all participants, but serum CEA concentration in different age groups show significant difference **(Table1)**. The scatter plots of CEA concentration and age showed serum CEA concentration increased mainly above the age of 20 years in all participants **(Figure 1)**.

Comparative analysed CSF and serum concentration revealed that CSF CEA concentrations were no higher than serum CEA concentrations in all participants, equal to serum CEA concentrations only in 0.84% (2/238) of participants, and lower than serum CEA concentrations in 99.16% (236/238) of participants. The ratio of the CEA level (CSF/serum) was from 0.017 to 1.

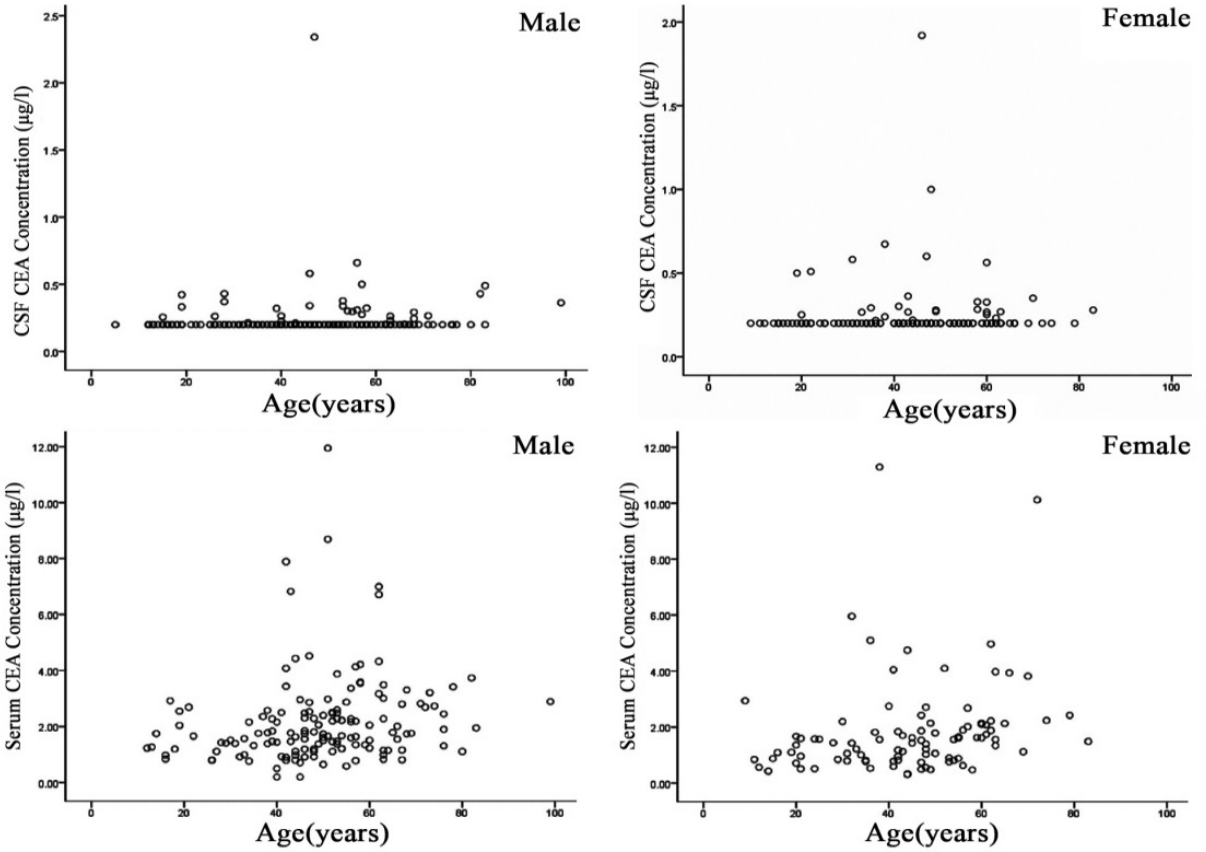

Figure 1. *The CSF and serum CEA concentrations in male and female participants in relation to age.*

Discussion

To establish the reference value for CSF CEA, the optimal subjects should be healthy. However, it is ethically infeasible to get CSF samples from healthy people through lumbar puncture for the sole purpose of this study. Therefore, only patients among whom lumbar puncture was warranted by their clinical condition were recruited. Theoretically, the diseases diagnosed in this study have no effects on the secretion of CEA; however, several of them, such as meningitis, increase the permeability of the BBB. Because an intact BBB has only a very slight effect on CSF CEA level [15], it is reasonable to apply the reference value established in this study to healthy people.

The value most frequently used as the upper reference limit of CSF CEA is the upper reference value for serum CEA which changes according to different methods in different laboratories [16]. Roche Modular Analytic E170 analyser was used in our laboratory and the upper reference value for serum CEA was 5µg/L. The results of our study showed that in most participants, CSF CEA was within extremely low levels. In all participants, the 97.5th percentile and even the maximum value of CSF concentrations were far lower than the reference value of 5µg/L. The results of current study suggest that the previously used reference value might result in an abnormally elevated CSF CEA concentration being considered normal. Serum CEA concentration increased mainly above the age of 20 years in all participants. However, such an increase was not found in the CSF CEA concentration in either the female or male participants.

Comparative measurement of CSF CEA and serum CEA revealed a phenomenon that has been reported that when the serum-to-CSF ratio is less than 60:1, an increase in CSF CEA level has a relatively high specificity for leptomeningeal metastasis [17]. Our study had CEA serum to CSF ratios ranging from 1 to 59.75. According to our study, CSF CEA concentrations were lower than serum CEA concentrations in most participants. However, we cannot conclude that CSF CEA concentrations in most people are lower than the corresponding serum CEA concentrations because the method used to measure CSF CEA in this study was specifically

developed to measure CEA in serum samples. Despite the limitations of this study, our findings were still useful to interpret the results of comparative measurements of serum and CSF CEA for clinical purposes.

Previous studies have found that CEA levels were significantly higher in leptomeningeal metastasis patients and CSF CEA is useful for diagnosing leptomeningeal metastasis [13,14,18].The results of our study provide new knowledge in the detection of abnormal levels of intrathecal CEA secretion through two aspects. First, the upper reference limit of CSF CEA might be lower than that used in clinical practice, which means that the sensitivity of the CSF CEA measurement in diagnosing brain metastasis and meningeal carcinomatosis might have been underestimated. When a CSF CEA concentration above the reference value proposed in this article is detected, abnormal intrathecal CEA secretion should be suspected, although it may not necessarily exist. Subsequently, further ancillary tests should be performed to ascertain or rule out brain metastasis and meningeal carcinomatosis. Secondly, although seen in a very small proportion of study samples, a CSF CEA concentration could have a quantitative value equal to a simultaneous serum CEA concentration.

There are some limitations warranting consideration in this study. First, it should be noted that our findings should only be applied to lumbar CSF and not to ventricular CSF, which we have not studied. Secondly, it should also be pointed out that our findings are method-specific. Whether our findings are applicable for interpreting the results of other investigators depends on the methods of CEA assay they use.

In summary, we propose an upper reference limit of CSF CEA lower than previously used, which might increase the sensitivity of measurement of CSF CEA in the detection of abnormal intrathecal CEA secretion.

Acknowledgment

This study was supported by Hainan applied technology development and demonstration projects (ZDXM2015088).

References

1. Baiges-Octavio JJ, Huerta-Villanueva M. Meningeal carcinomatosis. Rev Neurol 2000;31:1237-1241.
2. Van Oostenbruegge RJ, Twijnstra A. Presenting features and value of diagnostic procedures in leptomeningeal metastases. Neurology 1999;53:382–385.
3. Glass JP, Melamed M, Chernik NL, Posner JB. Malignant cells in cerebrospinal fluid (CSF): the meaning of a positive CSF cytology. Neurology 1979;29:1369–1375.
4. Corsini E, Bernardi G, Gaviani P, Silvani A, de Grazia U, Ciusani E, Croci D, Salmaggi A.Intrathecal synthesis of tumor markers is a highly sensitive test in the diagnosis of leptomeningeal metastasis from solid cancers. Clin Chem Lab Med. 2009;47:874-9.
5. Dhar P, Moore T, Zamcheck N, Kupchik HZ. Carcinoembryonic antigen (CEA) in colonic cancer. Use in preoperative and postoperative diagnosis and prognosis. JAMA 1972;221:31-35.
6. Holyoke ED. Present and probable uses of CEA. CA-Cancer J Clin1975; 25:22-26.
7. Persijn JP, Korsten CB, Batterman JJ, Tierie AH, Renaud J.Clinical significance of urinary carcino-embryonic antigen estimations during the follow-up of patients with bladder carcinoma or previous bladder carcinoma. Clinical evaluation of carcino-embryonic antigen, III. J Clin Chem Clin Biochem1976;14:395-399.
8. Kalser MH, Barkin JS, Redlhammer D, Heal A. Circulating carcinoembryonic antigen in pancreatic carcinoma. Cancer 1978;42:1468-1471.
9. Loewenstein MS, Rittgers RA, Feinerman AE, Kupchik HZ, Marcel BR, Koff RS, Zamcheck N. Carcinoembryonic antigen assay of ascites and detection of malignancy. Ann Intern Med 1978;88:635-638.
10. Noris-García E, Escobar-Pérez X. Brain metastasis and the carcinoembryonic antigen. Rev Neurol 2004;38:267-270.
11. Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. Cancer Treat Rev 1999;25:103-119.
12. van Zanten AP, Twijnstra A, Ongerboer de Visser BW, van Heerde P, Hart AA, Nooyen WJ. Cerebrospinal fluid tumour markers in patients treated for meningeal malignancy. J Neurol Neurosurg Psychiatry 1991;54:119-123.
13. Shi Q, Pu CQ, Wu WP, Huang XS, Yu SY, Tian CL, Huang DH, Zhang JT. Value of tumor markers in the cerebrospinal fluid in the diagnosis of meningeal carcinomatosis. Nan Fang Yi Ke Da Xue Xue Bao 2010;30:1192-1194.
14. Shi Q, Pu CQ, Huang XS, Tian CL, Cao XT.Optimal cut-off values for tumor markers in cerebrospinal fluid with ROC curve analysis. Front Biosci (Elite Ed) 2011;3:1259-1264.
15. Domaniewski J, Balcar-boron A, Wysocki M, Sujkowska R, Cetnarowski M, Szaflarska M, Gajny W, Makuch D. 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. Acta Paediatr Hung 1986;27:115-121.
16. Uhl W, Chan DW, Jones K, Kelley C, Assmann G, von Eckardstein A, Sägers A, Yvert JP, Schneider AM, Torralba A, Fuentes-Arderiu X, Gonzalez de la Presa B,Vives M, Greiling H, Eberle A, Niederau CM, Cremer P, Reiter W, Vogeser M, Neumeier D, Luppa P, Huber U. Elecsys CEA, PSA and AFP. Clinical results of a multicentre evaluation. Wien Klin Wochenschr 1998;110:51-61.
17. Jacobi C, Reiber H, Felgenhauer K. The clinical relevance of locally produced carcinoembryonic antigen in cerebrospinal fluid. J Neurol 1986;233:358-361.
18. Kang SJ, Kim KS, Ha YS, Huh SY, Lee JH, Kim JK, Kim MJ. Diagnostic value of cerebrospinal fluid level of carcinoembryonic antigen in patients with leptomeningeal carcinomatous metastasis. J Clin Neurol 2010;6:33-37.