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The Prognostic Role of Gama Glutamil Transferase in High Grade Glial Tumors

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Abstract

Purpose: Serum gamma-glutamyltransferase (GGT) has been shown to be associated with prognosis in various malignancies. However, it's prognostic role in high-grade gliomas has not been evaluated. In our study, the prognostic role of GGT in high-grade glial tumors was investigated.

Patients and Methods: We retrospectively evaluated 76 patients who were operated for high grade glioma in our center. In the pre-operation stage, blood biochemistry analyzes including routine complete blood count included lymphocyte count, liver (AST, ALT, GGT), LDH and kidney (BUN, Cre) function tests were implemented in all of our patients. Survival rates were calculated using the Kaplan-Meier survival analysis method.

Results: A total of 75 patients, 33 (44%) female and 56 (56%) male, were included in the study. The median age was 50±16.3 (range 15-85). Tumor location information could not be obtained in 13 of the patients. While gross total excision was implemented in 24 (53.3%) patients and sub-total excision was implemented in 26 (37.8%) patients, biopsy was implemented in 15 (20%) patients. The median follow-up period of the patients was 12.6 months (Range 0.07-54.5). A statistically significant correlation was found between GGT and survival (p=0.045).

Conclusion: Our results suggest that preoperative serum GGT is a prognostic factor for the survival of patients with high-grade glial tumors. Therefore, treatment strategies targeting GGT seem to be promising for this high-grade glial tumor.

Introduction

High-grade gliomas are the most common primary malignant brain tumors in adults. Malignant, that are classified according to their histopathological and molecular features as anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma) and glioblastoma often rapidly progressive brain tumors. Patients typically come up with subacute neurological signs and symptoms that progress over days or weeks and vary according to the location of the tumor in the brain. Despite advances in treatment, the median survival of patients is 12-15 months. The high mortality has led to the search for other factors that contribute to the prognosis.

Many clinicopathological and molecular prognostic factors have been investigated in high-grade gliomas. Age, Karnofsky performance score, complete reception of the radiotherapy program, and maximal surgical resection were found to be statistically significant clinicopathological factors. Presence of EGFR amplification, MGMT methylation, and IDH1 mutation status are significant molecular markers [1]. Gamma-glutamyltransferase (GGT) enzyme activity is commonly found in living organisms, including plants, yeasts, and bacteria. Gamma glutamyl transferase (GGT) is a cell surface glycoprotein composed of two dissimilar subunits. The most important source of GGT in serum is the liver. In addition, it is synthesized in high amounts in kidney tubules, biliary epithelium and brain capillaries. The main task of gamma glutamyl transferase in the cell is to break down the reduced glutathione found outside the cell and to provide precursor amino acids for intracellular glutathione synthesis [2]. Glutathione is the most abundant antioxidant molecule in cells and is involved in a variety of critical cellular functions such as detoxification of xenobiotics and/or their metabolites, modulation of cell proliferation, apoptosis and fibrogenesis [3].

It has been shown that there is a positive log-linear relationship between cancer risk and GGT levels. At the same time, it has been suggested that high serum GGT levels may be a poor prognostic factor in many cancer types such as lung, breast, esophagus, endometrial, cervix, ovary, kidney, stomach and colorectal [2]. There are conflicting reports between cancer patients' survival and GGT activity in studies. While some studies have reported that elevated GGT levels decrease survival, some studies have reported no such relationship. In our study, the prognostic role of GGT in high-grade glial tumors was investigated.

Methods

Patients with histopathologically confirmed diagnosis of high-grade glioma in Medical Park Gaziantep Hospital between 2014 and 2018 were included in the study. However, patients with active bleeding, bleeding diathesis, hyper or hypothyroidism, infection, previous gallbladder or bile duct surgery, disseminated intravascular coagulation, heparin therapy, or connective tissue disease who have received blood transfusion in the last 3 months and patients with chronic alcohol use were excluded from the study. The stage of the disease and the treatment information were obtained by retrospectively reviewed from medical records. In pre-operation stage, blood biochemistry analyzes including routine complete blood count including lymphocyte count, liver (AST, ALT, GGT), LDH and kidney (BUN, Cre) function tests were implemented in all our patients.

Statistical Analyses

Statistical analyzes were performed using SPSS version 15.0 software. Examination of survival with univariate analyzes was performed with the log rank test. In multivariate analysis, independent factors in predicting survival were examined using Cox regression analysis by using possible factors identified in previous analyzes. Survival rates were calculated using the Kaplan-Meier survival analysis method. It was interpreted as statistically significant that the Type-1 error level was below 5%.

Results

A total of 75 patients, 33 (44%) female and 56 (56%) male, were included in the study. The median age of the patients was 50±16.3 (range 15-85). When the patients were evaluated according to the ECOG performance score, ECOG 0 was detected in 62 (82.7%), ECOG 1 8 (10.7%) and ECOG 2 5 (6.6%) patients. Fifteen of the patients had comorbid disease. The most common comorbid diseases were Type 2 diabetes mellitus with 4 patients and essential hypertension in 5 patients. The coexistence of diabetes and hypertension was detected in 2 patients.

When the patients were evaluated according to their first clinical presentation, it was found that they presented with the most common neurological deficit, 23 (30.7%) patients. This was followed by headache 20 (26.7%), epileptic attack 11 (114.7%), syncope 6 (8%) patients. Primary glioblastoma was detected in 73 (97.3%) of the patients, while secondary glioblastoma was detected in 2 (2.7%) patients. While the tumor was located on the left side in 30 (40%) of the patients, it was located on the right side in 40 (40%) patients. The tumor location was in the frontal lobe in 27 (36%), temporal lobe 15 (20%), and occipital lobe 6 (8%) patients in the posterior fossa. Tumor location information could not be obtained in 13 of the patients. While gross total excision was performed in 24 (53.3%) patients and sub-total excision was performed in 26 (37.8%) patients, biopsy was performed in 15 (20%) patients. The median follow-up period of the patients was 12.6 months (Range 0.07-54.5). A statistically significant correlation was found between GGT and survival (p=0.045) (Figure 1).

Discussion

Many studies have shown that GGT has an important role in reducing events such as antioxidant/antitoxic defense and cell proliferation/apoptosis balance in the cell. GGT is also thought as a factor that provides growth and survival advantages for fast-growing neo-plastic cells. In our study, we observed that high GGT levels worsened survival. There is a high amount of GGT in brain capillaries. It is suggested that low levels of hydrogen peroxide, which occurs as a byproduct of GGT activity, may act as a kind of 'signal-to-life' by maintaining cell proliferation and protecting against apoptosis, possibly through upregulation of PARP activity [4,5]. At the same time, it can act as a kind of extracellular detoxification mechanism by binding chemotherapeutics such as cysteine-glycine and cisplatin, which are formed because of GGT activity [6].

The prognostic role of GGT has been studied in many malignancies. Su et al. [7] investigated the relationship between preoperative GGT levels and survival in patients who underwent radical cystectomy for bladder cancer [7]. In their study, they stated that preoperative GGT level is an independent prognostic factor for survival. Therefore, they suggested that it can be used in prognostic models for bladder cancer. Staudigl et al. [8] investigated the relationship between pretherapeutic GGT levels and prognosis in patients with primary metastatic breast cancer [8]. They did not detect any association with indicators of aggressive tumor biology such as pre-treatment GGT levels, HER2 status, triple-negative histology, or poorly differentiated cancers. They found that higher GGT level was associated with worse survival. With these results, they suggested that pretherapeutic GGT levels can be used as a new prognostic factor. Similar studies have shown the prognostic role of GGT in hepatocellular cancer, ovarian cancer, prostate cancer, renal cell cancer, esophageal cancer and cervical cancer [9-14]. However, as far as we know, there are no studies examining the role of GGT in the prognosis of high -grade glial tumors.

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Cerebral endothelial cells form the selective permeability barrier between brain and blood, thanks to their tight junctions and the presence of special carrier systems. Risau et al. [14] showed that blood-brain barrier pericytes are the main source of gamma-glutamyl transpeptidase activity in brain capillaries [15]. In glial tumors with increased angiogenesis, pericyte-derived GGT may show more aggressive tumor histology as an indicator of angiogenesis. GGT2 has been shown to play a role in the transport of amino acids across the blood brain barrier [16]. The variation in amino acid concentrations also explains why high GGT levels are associated with poor prognosis. However, this issue needs to be supported by further studies.

GGT can also increase oxidative stress in certain situations. Persistent oxidative stress leads to genomic instability and cell proliferation, following the imbalance of apoptosis involved in carcinogenesis and progression [17]. Therefore, GGT can be used as an indicator of tumor aggressiveness as an indicator of the severity of oxidative stress. It has been reported that GGT can be induced by various inflammatory factors including tumor necrosis factor and interferon [18,19].

Although, we found in our study that high GGT levels worsened survival, our study has some limitations. First, this was a single-institution retrospective study with limited patients, potential selection bias cannot be excluded. Second, due to the retrospective design, some data may have been overlooked and collected inaccurately, and they may have affected the results. Third, the median follow-up time for all patients was 12.6 months, which may be insufficient especially for grade 3 patients. Fourth, the best threshold value of serum GGT has not been determined. In our study, the cut-off point of GGT preoperatively was taken as 40 U/L. The best cut-off value of serum GGT should be determined. Therefore, the results of our study should be confirmed by well-designed independent multicenter studies with adequate follow-up time.

Conclusion

GGT was viewed solely as an enzyme that promoted the recovery of extracellular cysteine. Clinically, it was only seen as a biomarker of hepatobiliary disease and chronic alcohol use. However, today in many experimental and clinical studies, GGT-mediated cleavage of gamma-glutamyl bonds is the first step of a series of reactions that can modulate the redox balance in and around the cell, and this shows that it can be effective in the pathophysiology of many diseases. Therefore, GGT activity has been identified as a potential target for the treatment of various disease conditions. We think that GGT may be a prognostic marker in high-grade glial tumors and that therapies targeting GGT can contribute to the treatment of high-grade glial tumors.

References

1. Alonso D, Matallanas M, Riveros-Perez A Alba Riveros-Perez, Maripaz Perez-Payo, et al. (2017) Prognostic and predictive factors in high-grade gliomas. Neurocirugia (Astur) 28(6): 276-283.
2. Bozkaya Y, Yazıcı O (2019) Prognostic significance of gamma-glutamyl transferase in patients with metastatic non-small cell lung cancer. Expert Rev Mol Diagn 19(3): 267-272.
3. Forman HJ, Zhang H, Rinna A (2009) Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med 30(1-2): 1-12.
4. Kunutsor SK, Apekey TA, Van Hemelrijck M Giliola Calori, Gianluca Perseghin (2015) Gamma glutamyltransferase, alanine aminotransferase and risk of cancer: systematic review and meta-analysis. Int J Cancer 136(5): 1162-1170.
5. B del Bello, Paolicchi A, Comporti M A Pompella, E Maellaro (1999) Hydrogen peroxide produced during gamma-glutamyl transpeptidase activity is involved in prevention of apoptosis and maintainance of proliferation in U937 cells. FASEB J 13(1): 69-79.
6. Ahmad S, Okine L, Wood R, J Aljian, D T Vistica (1987) Gamma-Glutamyl transpeptidase (gamma-GT) and maintenance of thiol pools in tumor cells resistant to alkylating agents. J Cell Physiol 131(2): 240-246.
7. Su S, Liu L, Sun C, Yanhua Nie, Hong Guo, et al. (2021) Preoperative Serum Gamma-Glutamyltransferase as a Prognostic Biomarker in Patients Undergoing Radical Cystectomy for Bladder Cancer. Front Oncol 11: 648904.
8. Staudigl C, Concin N, Grimm C, Georg Pfeiler , Regina Nehoda , et al. (2015) Prognostic relevance of pretherapeutic gamma-glutamyltransferase in patients with primary metastatic breast cancer. PLoS One 10(4): 0125317.
9. Xu XS, Wan Y, Song SD, Wei Chen, Run-Chen Miao et al. (2014) Model based on γ-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis World J Gastroenterol 20(31): 10944-10952.
10. Takemura K, Ito M, Nakanishi Y, Madoka Kataoka, Kazumasa Sakamoto et al. (2019) Serum γ-Glutamyltransferase as a Prognostic Biomarker in Metastatic Castration-resistant Prostate Cancer Treated with Enzalutamide. Anticancer Res 39(10): 5773-5780.
11. Luo C, Xu B, Fan Y, Yu W, Wei Yu, Qian Zhang et al. (2017) Preoperative Gamma-Glutamyltransferase ıs associated with cancer-specific survival and recurrence-free survival of nonmetastatic renal cell carcinoma with venous tumor thrombus. Biomed Res Int 2017: 3142926.
12. Yang F, Zhang S, Yang H, K Luo, J Wen et al. (2015) Prognostic significance of gamma-glutamyltransferase in patients with resectable esophageal squamous cell carcinoma. Dis Esophagus 28(5): 496-504.
13. Strasak AM, Goebel G, Concin H, Ruth M Pfeiffer, Larry J Brant, et al. (2010) Prospective study of the association of serum gamma-glutamyltransferase with cervical intraepithelial neoplasia III and invasive cervical cancer Cancer. Res 70(9): 3586-3593.
14. Risau W, Dingler A, Albrecht U, M P Dehouck, R Cecchelli, et al. (1992) Blood-brain barrier pericytes are the main source of gamma-glutamyltranspeptidase activity in brain capillaries. J Neurochem 58(2): 667-672.
15. Hawkins RA, O'Kane RL, Ian A Simpson, Juan R Viña et al (2006) Structure of the blood-brain barrier and its role in the transport of amino acids J Nutr 136(1 Suppl): 218S-226S.

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16. Corti A, Franzini M, Paolicchi A, Alfonso Pompella (2010) Gamma-glutamyltransferase of cancer cells at the crossroads of tumor progression, drug resistance and drug targeting. Anticancer Res 30(4): 1169-1181.

17. Bouman L, Sanceau J, Rouillard D, Brigitte B (2002) Gamma-Glutamyl transpeptidase expression in Ewing's sarcoma cells: up-regulation by interferons Biochem J 364(3): 719-724.

18. Daubeuf S, Accaoui MJ, Pettersen I, N E Huseby, A Visvikis, et al. (2001) Differential regulation of gamma-glutamyltransferase mRNAs in four human tumour cell lines. Biochim Biophys Acta 1568(1): 67-73.

19. Corti A, Belcastro E, Dominici S, Emilia Maellaro, Alfonso Pompella, et al. (2020) The dark side of gamma-glutamyltransferase (GGT): Pathogenic effects of an 'antioxidant' enzyme. Free Radic Biol Med 160: 807-819.

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