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Research Article

Dissociation of Correlations Between Aggregation Indicators and the Number of Peripheral Blood Cells with Regenerative Potential Contributes to an Increase in Life Expectancy et Glioblastomas

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Abstract

The work investigated the correlations between the indicators of blood cells aggregation, characterizing stage II inflammation, and their quantitative composition in the peripheral blood, in patients before and after surgery for the total removal of glioblastomas. A very high correlation coefficient was found in patients with preoperative glioblastomas. After total removal of the tumor, the indices of the number of blood cells and the level of cell aggregation lost reliable correlations on the 7th day after the operation. They were also absent in healthy individuals. It is assumed that the growth of a tumor in the body is to a certain extent due to the functioning of blood cells with a regenerative potential against the background of a pronounced inflammatory process, which is confirmed by high rates of correlations. The absence of such connections after removal of glioblastomas and in healthy individuals may contribute to a new approach to the development of a method for diagnosing malignant brain tumors, which is difficult due to the presence of the blood-brain barrier and the rapid development of edema in the perifocal areas of the brain. A significant decrease in the manifestations of the inflammatory process against the background of regeneration processes in the postoperative period, as well as high correlations between the cells themselves with a regenerative potential, restoring the cytoarchitectonics of brain tissues, can probably contribute to an increase in the life expectancy of patients with glioblastomas.

Keywords: *Glioblastomas; Inflammation; Blood Cells Number and Aggregation; Negative Correlation; Diagnostic Method; Increase in Life Expectancy.*

Introduction

The study of glioblastomas at the systemic level suggests that in the progression of the growth of these tumors, one of the mechanisms is a competitive relationship between reparative and regenerative processes in the body. These processes are separated from each other both in time and in space by the mechanisms of apoptosis and epithelial-mesenchymal transition (EMT) [1-4]. These mechanisms protect the regenerative processes carried out by stem cells from the influence of unfavorable factors on them during the inflammatory process [5-8]. Of scientific interest are data that hematopoietic stem cells (HSCs) can have a high regenerative potential [9]. In addition, HSCs also have a high potential for directed migration to glioma cells [9]. It has been proven that from the bone marrow stem cells of hematogenous origin migrate, which can differentiate into neurons and glia, replacing defects in tissues of tumor and non-tumor genesis [10-15].

Probably, all these cells, using the growth factors that they synthesize, contribute to the renewal of tumor tissue, stimulating its growth, vascularization, invasion into adjacent tissues, etc. performing a protective and compensatory function in response to the partial death of the tumor mass. It can be assumed that one of the stimuli for the further growth and progression of gliomas may be chronic aseptic inflammation, which is the triggering mechanisms of all the above processes**.**

The above data confirm the facts about the close relationship of the functions of peripheral blood cells with the mechanisms of tumor growth and the associated inflammatory process, characterized by an increased level of aggregation of blood cells. The analysis of such a relationship may be of scientific interest in the study of the mechanisms of tumor progression, practical interest in the development of new methods for the diagnosis of intracerebral tumors and suppression of tumor growth.

Malignant brain tumors are particularly difficult in the diagnosis of primary tumors, because they are isolated due to the blood-brain barrier, which largely prevents the entry of tumor markers into the bloodstream. The use of imaging methods for determining tumors in the brain is often hampered by the presence of an inflammatory process that promotes the formation of local edema in the tumor focus, and some other factors. The work proposes the development of a new method for the diagnosis of malignant tumors in the barrier space without the use of molecular tumor markers determined in the peripheral blood or tumor tissues. This method can be applied in practice as a result of its simplicity and availability with repeated monitoring.

Researchers are studying the relationship between the number of various cells in peripheral blood, which is of certain scientific interest from the point of view of diagnosing tumor processes in the body of patients [16-22].

This work was the first to compare the correlations between the indicators of the level of aggregation of blood cells, which determine stage II of the inflammatory process, and peripheral blood cells with regenerative properties in the tumor focus, such as leukocytes, lymphocytes and monocytes. The work was carried out in patients with brain glioblastomas before surgery and on the 7th day after total tumor resection.

Aim of the Study

Investigation of the role of correlation dissociation between indicators of increased aggregation of blood cells and their number in the peripheral blood in increasing the life expectancy of patients with glioblastomas.

Materials and Methods

Patients (38 people) were admitted to the clinic of the State Institution "Institute of Neurosurgery named after acad. AP Romodanov NAMS of Ukraine" with intracerebral tumors. Among those admitted, 25 patients were with initially diagnosed intracerebral tumors and 13 patients with continued tumor growth. The control group of 10 people consisted of practically healthy people.

Method of blood cells aggregation determination: To objectify the presence of inflammation in the body of a patient with a brain tumor, we used the determination of aggregation of blood cells (stage II of the inflammatory process). The indicators of the level of aggregation of blood cells were determined on a highly sensitive biosensor device "Plasmon", designed using the physical phenomenon of surface plasmon resonance (SPR) [23]. Modification of the level of aggregation of blood cells by adding to blood cells 0.25% verapamil hydrochloride ("Farmak" company) in low concentrations, when diluted with distilled water 100 times, significantly contributed to the determination of the presence of an inflammatory process in patients with glioblastomas [24,25]. Samples of blood cells with the addition of distilled water in the same volume as when diluting verapamil hydrochloride (10 µl diluted 100 times 0.25% verapamil hydrochloride and 100 µl H2O) served as a control. The level of aggregation of blood cells was determined in units of SPR.

Method for determination of blood cells number: The number of blood cells was determined in the same blood samples using a Mindray-3000 automatic hematological analyzer. Monocytes were detected in the pool of Mid cells of the peripheral bloodstream.

After surgical removal, all tumors were histologically verified as isomorphic cell glioblastomas. In the work, we used the indicators obtained in patients with total removal of glioblastomas, which was verified by imaging research methods.

Statistical studies were performed using the "Statistics-10v" package.

Method for determining the correlation coefficient

Spearman's rank correlation coefficient was used as a measure of the relationship between the variables, which ranges from -1 to + 1. If less than 0.25 the correlation is weak, from 0.25 to 0.75 it is moderate, and if it is more than 0.75 it is strong. The statistical significance of the obtained coefficient is assessed using the Student's t-test. Checking the significance of the correlation coefficient, establishes the presence or absence of a correlation between the studied indicators.

Results and Discussion

Healthy people	Spearman Rank Order Correlations Marked correlations are significant at p <,05000			
	WBC	Lymph	Mid	Gran
Control -erythr. + H_2O	-0,20	-0,07	-0,64	0,28
Verapamil hydr. - 1:100 dilution	-0,06	0,07	-0,37	0,33

Table 1: *Correlation coefficients between the number of peripheral blood cells and indicators of their aggregation in practically healthy individuals.*

Patients with glioma IV before surgery	Spearman Rank Order Correlations MD pairwise deleted Marked correlations are significant at p <,05000			
	WBC	Lymph	Mid	Gran
Control -erythr. + H_2O	-0,62	-0,36	-0,70	-0,61
Verapamil hydr. - 1:100 dilution	-0,94	-0,77	-0,83	-0,77

Table 2: *Correlation coefficients between the number of peripheral blood cells and indicators of their aggregation in patients with glioblastoma before surgery.*

Patients with glioma IV after surgery	Spearman Rank Order Correlations Marked correlations are significant at p <,05000			
	WBC	Lymph	Mid	Gran
Control -erythr. + H_2O	0,17	-0,10	0,07	0,12
Verapamil hydr. - 1:100 dilution	-0,04	0,13	-0,41	-0,25

Table 3: *Correlation coefficients between the number of peripheral blood cells and indicators of their aggregation in patients with glioblastoma after surgery (7 days).*

In the group of healthy individuals (Table 1) and in patients on the 7th day after total tumor removal (Table 3), no correlation was found between the SPR indices and the number of blood cells. Consequently, in the absence of a tumor in the body, there is no correlation between the inflammatory process and blood cells with a regenerative potential.

In the group of patients before surgery to remove glioblastoma (Table 2), high correlations were found between the number of leukocytes and monocytes (Mid) and the level of blood cell aggregation (SPR) in the control (with the addition of distilled water) and with

the addition of verapamil- hydrochloride preparations to the blood at a dilution of 1: 100. Lymphocytes and granulocytes also showed a high level of correlation with verapamil- hydrochloride (1: 100), but in the group of patients studied in the work, it is not yet reliable. The indicator of blood cell aggregation upon the addition of 0.25% verapamil-hydrochloride diluted 100 times reliably determined the presence of an inflammatory process in the body not associated with tumor growth [24].

Healthy people	Spearman Rank Order Correlations Marked correlations are significant at p <,05000			
	WBC	lymph	Mid	Gran
WBC	1,00	0,51	0,56	0,76
Lymph	0,51	1,00	0,52	0,03
Mid	0,56	0,52	1,00	0,15
Gran	0,76	0,03	0,15	1,00

Table 4: *Correlation coefficients between the number of peripheral blood cells in practically healthy individuals.*

Before surgery	Spearman Rank Order Correlations MD pairwise deleted Marked correlations are significant at p <,05000			
	WBC	Lymph	Mid	Gran
WBC	1,00	0,88	0,84	0,94
Lymph	0,88	1,00	0,63	0,88
Mid	0,84	0,63	1,00	0,81
Gran	0,94	0,88	0,81	1,00

Table 5: *Correlation coefficients between the number of peripheral blood cells in patients with glioblastoma before surgery.*

After surgery (7-th day)	Spearman Rank Order MD pairwise deleted Marked correlations are significant at p <,05000			
	WBC	Lymph	Mid	Gran
WBC	1,00	0,72	0,90	0,87
Lymph	0,72	1,00	0,41	0,38
Mid	0,90	0,41	1,00	0,91
Gran	0,87	0,38	0,91	1,00

Table 6: *Correlation coefficients between the number of peripheral blood cells in patients with glioblastoma after surgery (7 days).*

Table 4 in healthy individuals shows a high correlation between cells of the leukocyte and granulocyte pools.

In patients before surgery to remove a brain tumor, high correlation rates exist between leukocytes and other cells; between lymphocytes and leukocytes, monocytes, granulocytes; in monocytes and granulocytes between all other cells. Consequently, in patients before surgery against the background of an inflammatory process, all studied cells interact with each other, as indicated by high correlations.

On the 7th day after surgery, correlations between monocytes and granulocytes with lymphocytes disappear in the cell ensemble of patients against the background of the absence of correlations with the inflammatory process with the total removal of glioblastomas and

the absence of necrotic tumor tissues. These data may indicate the end of pronounced inflammatory manifestations and the beginning of the development of regenerative mechanisms with the participation of cells of the monocytic pool.

It was previously shown that the systematic suppression of the inflammatory process in patients with glioblastomas in the postoperative period contributes to an increase in their life expectancy [24,25]. Continuation of these studies showed results in which the average life expectancy increased up to 22 months after surgery, compared with the average (9 months) in the group in which anti-inflammatory measures were not taken (Table 7 and figure 1).

Group	Number	Mean	Standard error of mean	Median life expected
Control	39	9,30	1,04	8,00
Verapamil	13	22,46	2,23	19,00

***Table 7**: Life expectancy of patients with glioblastomas in the postoperative period with using of verapamil- hydrochloride in low concentrations in order to inhibit the inflammation process.*

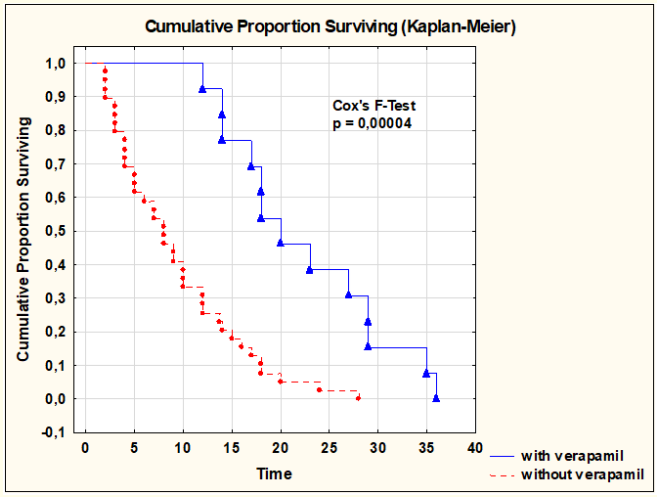

***Figure 1:** Life expectancy of patients after removal of glioblastomas during treatment with verapamil-hydrochloride and in the control group.*

Conclusion

The studies have shown that with more effective suppression of inflammation, along with total removal of the tumor, the correlation of the regenerative processes by cells with the regenerative potential can contribute to the fact that the results of the life expectancy of patients with glioblastomas are significantly increased. So, in our interim, not yet completed studies, they increased by an average of 22 months in comparison with the control indicators, which correlated with the data of the National Cancer Registry of Ukraine [26]. Some patients live more than 3 years, while in the control group of patients without verapamil- hydrochloride treatment, such indicators were absent.

Bibliography

1. Thiery JP. "Epithelial-mesenchymal transitions in tumour progression". *Nature Reviews Cancer* 2.6 (2002): 442-454.

2. Polyak K and Weinberg RA. "Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits". *Nature Reviews Cancer* 9 (2009): 265-273.

3. Bedi U., *et al*. "Epigenetic plasticity: a central regulator of epithelial-to-mesenchymal transition in cancer". *Oncotarget* 5.8 (2014): 2016-2029.

4. Shvachko LP and Kholod OV. "Epithelial-mesenchymal transition in carcinogenesis". *Oncology* 16.1 (2014): 4-12.

5. Fernandes JV., *et al*. "The role of the mediators of inflammation in cancer development". *Pathology and Oncology Research* 21.3 (2015): 527-34.

6. Moore MM., *et al*. "Inflammation and cancer: causes and consequences". *Clinical Pharmacology and Therapeutics* 87. 4 (2010): 504-508.

7. Shigdar S., *et al*. "Inflammation and cancer stem cells". *Cancer Letters* 345 (2014): 271-278.

8. Tanno T and Matsui W. "Development and Maintenance of Cancer Stem Cells under Chronic Inflammation". *Journal of Nippon Medical School* 78. 3 (2011): 138-145.

9. Bryukhovetskiy IS., *et al*. "Substantiation in an *in vitro* experiment of the phenomenon of directed migration of hematopoietic stem and progenitor cells of adult mammals to rat glioma cells of the C6 line". *Bulletin of the Russian Oncology Center N.N. Blokhin RAMS* 25.1-2 (2014): 31-38.

10. Beachy PhA., *et al*. "Tissue repair and stem cell renewal in carcinogenesis". *Nature* 432 (2004): 324-331.

11. Eglitis MA and Mezey E. "Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice". *Proceedings of the National Academy of Sciences of the United States of America* 94 (1997): 4080-4085.

12. Abody KS., *et al*. "Neural stem cells display extensive tropism for pathology in adult brain: Evidence from intracranial gliomas". *Proceedings of the National Academy of Sciences of the United States of America* 97.23 (2000): 12846-12851.

13. Jiang Y., *et al*. "Pluripotency of mesenchymal stem cells derived from adult marrow". *Nature* 418. (2002): 41-49.

14. Bjorson ChRR., *et al*. "Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo". *Science* 283 (1999): 534-536.

15. Simara P., *et al*. "Reprogramming of Adult Peripheral Blood Cells into Human Induced Pluripotent Stem Cells as a Safe and Accessible Source of Endothelial Cells". *Stem Cells and Development* 27. 1 (2018): 10-22.

16. Zao Y., *et al*. "A human peripheral blood monocyte-derived subsets as pluripotent stem cells". *Proceedings of the National Academy of Sciences of the United States of America* 100. 5 (2003): 2426-243.

17. Sun Z., *et al*. "The roles of mesenchymal stem cells in tumor inflammatory microenvironment". *Journal of Hematology and Oncology* 7. 1 (2014): 2-21.

18. Han Sh., *et al*. "Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma". *Cancer* 15 (2015): 617.

19. Gu L., *et al*. "Prognostic role of lymphocyte to monocyte ratio for patients with cancer: evidence from a systemic review and meta-analysis". *Oncotarget* 7 (2016): 31926-31942.

20. Zadora P., *et al*. "Preoperative neutrophil-lymphocyte count ratio helps predict the grade of glial tumor – a pilot study". *Neurologia i Neurochirurgia Polska* 49 (2015): 41-44.

21. Zheng SH., *et al*. "Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study". *Journal of Neurosurgery* 3 (2017): 1-10.

22. Kemerdere R., *et al*. "Preoperative systemic inflammatory markers in low- and high-grade gliomas: A retrospective analysis of 171 patients". *Helion* 5 (2019): eO1681.

23. Gridina NYa. "Utilizing SPR as a Novel Technique to Measure Cell Aggregation for Ketamine Treated Brain Gliomas". *Cancer and Oncology Research* 1 (2013): 1-5.

24. Gridina NYa., *et al*. "Some aspects of the Systemic Mechanism of Brain Malignant Gliomas Progression and Methodological Approaches to its Correction". *EC Neurology* 12.4 (2020): 80-90.

25. Gridina NYa., *et al*. "Tumor-Associated Inflammation Mechanisms Correction by Verapamil at Brain Gliomas Progression". *European Journal of Pharmaceutical and Medical Research* 3.8 (2016): 73-78.

26. Rozumenko AV., *et al*. "Survival rates in patients with the newly diagnosed glioblastoma: Data from National Cancer Registry of Ukraine, 2008-2016". *Ukrainian Neurosurgical Journal* 2 (2018): 33-39.

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