Lipid Levels in Glioblastoma Multiforme and the Role of Ki 67 Index in the Determination of Proliferation Activation

Hladiny lipidů u glioblastomu a úloha indexu Ki 67 při určování aktivace proliferace

Abstract

Aims: The aim of this study was to look for an association between lipid levels and the Ki 67 index and the value of the Ki 67 index in the determination of proliferative activity in glioblastoma multiforme (GBM). *Materials and methodology:* Sixteen patients with GBM who had undergone surgical treatment were included in the study. Pre-operative magnetic resonance (MRI) and MRI spectroscopy investigations were performed on all the patients. The lipid levels of all patients were recorded. In pathological investigation, the ratio of the number of cells stained by Ki 67 nuclear staining to the number of all the cells was calculated in terms of a percentage. The association between lipid levels and the Ki 67 index of cases was analysed. *Results:* There was no significant relationship between age, gender and the Ki 67 index and lipid levels of cases. It was significant to have a value of 350 as the lowest lipid level in GBM. There was no significant relationship between the Ki 67 index and lipid levels. *Conclusions:* The Ki 67 index has no value in determination of a treatment strategy in cases diagnosed with GBM. Therefore, we do not believe that the Ki 67 index study should be a routine laboratory investigation in cases with GBM.

Souhrn

Cíle: Cílem této studie bylo hledat souvislost mezi hladinami lipidů a indexem Ki 67 a hodnotou indexu Ki 67 při určování proliferační aktivity multiformního glioblastomu (GBM). *Materiál a metodika:* Do studie bylo zařazeno 16 pacientů s GBM, kteří prodělali operativní léčbu. U všech pacientů byla provedena předoperační magnetická rezonance (MR) a MR spektroskopie. Hladiny lipidů u všech pacientů byly zaznamenány. Při patologickém vyšetření byl vypočítán procentuální poměr počtu buněk označených jaderným barvením Ki 67 a počtu všech buněk. Souvislost mezi hladinami lipidů a indexem Ki 67 v uvedených případech byla analyzována. *Výsledky:* V uvedených případech neexistoval žádný významný vztah mezi věkem, pohlavím a indexem Ki 67 a hladinami lipidů. Významné bylo dosažení hodnoty 350 jako nejnižší hodnoty lipidů při multiformním glioblastomu. Neexistoval žádný významný vztah mezi indexem Ki 67 a hladinami lipidů. *Závěry:* Index Ki 67 nemá žádný význam při určování léčebné strategie u pacientů s diagnostikovaným GBM. Proto se nedomníváme, že by studie indexu Ki 67 měla být rutinní součástí laboratorního vyšetření pacientů s GBM.

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Klíčová slova

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Introduction

It is important to know the proliferative activity of brain tumors before treatment, in order to decide the therapeutic strategy in patients with brain tumors. The Ki 67 index is an important marker for determination of the proliferative activities of glial tumors. However, the prognostic value of this index in cases of glioblastoma multiforme (GBM) is controversial. Furthermore, the Ki 67 index can be determined directly in the tissue. Hence, studies on the relationship between radiological findings and proliferative markers preoperatively have gained attention. MR Spectroscopy (MRS) has begun a new era. Investigations including MRS, choline (Cho), creatinine (Cr), N-Acetyl Aspartate (NAA), lactate and lipid levels are widely used, not only in the diagnosis of glial tumors, but in the grading of these tumors as well.

The aim of this study was to look for an association between lipid levels and the Ki 67 index and the value of the Ki 67 index in the determination of proliferative activity in cases with GBM. In contrast to that of the literature, we studied the lipid levels measured by MRS in cases with high grade astrocytomas.

Materials and methods

Sixteen patients with GBM who had undergone surgical treatment in the Neurosurgery Clinic of Firat University Medical Center were included in the study. None of the patients had previous histories of operations, radiotherapy or chemotherapy.

Radiological investigation

Pre-operative magnetic resonance imaging (MRI) and MRS investigations were performed on all the patients. MR investigations were performed using Siemens 1.5 T MRG. First, spinecho T2 sequences were obtained in the axial, coronal and sagittal plains. Voxel (voxel of interest) was implanted in the mass lesions. Voxel was set as signal noise ratio of 1. Spectras were obtained for TR/TE 1 500/30 and 1 500/135. The lipid levels of all patients were recorded.

Pathological investigation

The method of Karamitopoulou et al was used in the assessment of the Ki 67 proliferation index [1]. In the 400X field, 150–500 cells were counted. The ratio of the number of cells stained by Ki 67 nuclear staining to the number of all the cells was calculated in terms of a percentage.

Table 1. Ki 67 index and lipid levels of the patients.

Case No	Age	Gender	Ki 67 index (%)	Lipid level
1	59	F	13.84	975
2	40	F	21.2	1 309
3	55	M	30	1 001
4	56	M	36.9	1 349
5	34	M	34.7	983
6	68	M	50.4	1 020
7	66	F	20.63	365
8	79	M	38.17	1 300
9	44	M	50.2	1 279
10	76	F	20.81	350
11	64	F	32.84	1 348
12	42	M	39.9	380
13	58	F	31.7	395
14	46	M	10.6	1 250
15	61	M	35.63	970
16	53	F	50.4	1 018

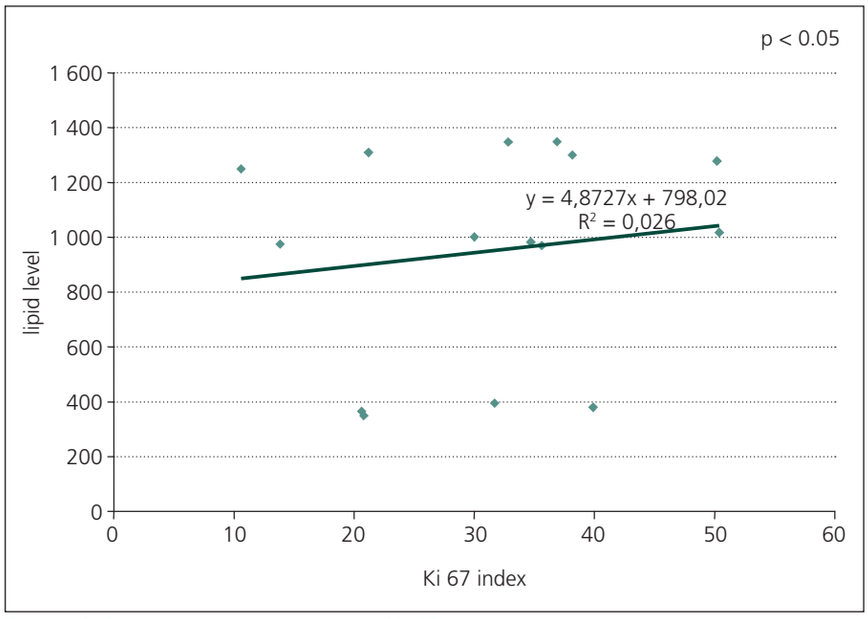

Figure 1. Relationship between the Ki 67 index and lipid levels.

Statistics

The SPSS program (SPSS for Windows; version 15.0; SPSS, Inc. Chicago, IL) was used for the statistical analysis. The Mann-Whitney Test was performed and the level of significance was set as $p < 0.05$.

Results

The mean age of the patients was 56 (range = 34–79; Table 1). The mean Ki 67 proliferation index of 16 patients with GBM was 30.14%. There was no significant relationship between age and gender and the Ki 67 index. The mean level of lipid calculated by MRS was as high as 879.81 ± 91.03. It is worth mentioning that the lowest lipid level observed in GBM was 350. There was no significant relationship between age, gender and lipid levels. The Ki 67 proliferation index and the lipid levels of the patients are presented in Table 1. There was no significant relationship between the Ki 67 index and lipid levels (Figure 1).

Discussion

While the Ki 67 non-histone nuclear protein can be detected in G1, S, G2 phases, in which the cell proliferation occurs, it cannot be detected in the silent G0 phase. Ki 67 activity is closely related to the tumor grade system [2]. It has been shown that the Ki 67 index is concordant with recurrence and prognosis, especially in low-grade glial tumors as it has prognostic value [3,4]. However, Wakimoto et al stated that it is an important prognostic factor for all grades of astrocytomas [5]. On the contrary, there have been reports stating that Ki 67 was not effective in estimating survival in astrocytic tumors [6]. Bouvier-Labit stated that Ki 67 staining had no prognostic value in the series that included only GBM [7]. However, although the Ki 67 index showed concordance with the tumor grade when low-grade and high-grade glial tumors were compared, it showed great variation in cases of GBM [8]. It is widely accepted that the Ki 67 index should be supported by additional factors to estimate the prognosis in GBM.

It is known that MRS helps tissue characterization of the lesions and that the combination of Cho/NAA, Cho/Cr ratios and the presence of lactate and lipid peaks are reliable in the staging of gliomas [9]. Byrd et al showed in their study, consisting of 75 patients with brain tumor, that aggressive tumors demonstrated higher levels of Cho, and were accompanied by increased lactate and lipid levels [10]. There is a relationship between the degree of necrosis in the tumor and the lipid level [11]. Negendank et al reported that the presence of lipid in the tumor may be an indicator of malignancy [12]. Similarly, Poptani et al reported that the presence of lipid showed a higher stage of malignancy [9]. The presence of necrosis is an important criterion for the diagnosis of GBM. We believe that comparing the Ki 67 index and lipid levels in GBMs may contribute to the discussions on the value of Ki 67 in determining the proliferative activation of the tumor.

In our study, the mean value for the Ki 67 proliferative index was 30.14%, and the mean lipid level was 879 ± 91.03 in 16 patients with GBM. Although it is expected that the Ki 67 index should increase as well as the lipid levels in more aggressive GBM cases, we could not find a significant relationship between lipid levels and Ki 67. Our result supports the thesis that the Ki 67 index is not significant in determination of proliferative activation when highgrade astrocytomas were the only group under study. Another important finding was the lack of a relationship between age or gender and Ki 67 and lipid levels in cases of GBM. However, this finding should be supported by a larger series.

Consequently, when elevated lipid levels in MRS, which is associated with the diagnosis of more aggressive tumors, are taken as the basis, the Ki 67 index does not contribute to determination of proliferation activation in GBMs. In other words, the Ki 67 index has no value in determination of a treatment strategy in cases diagnosed with GBM. Therefore, we do not believe that the Ki 67 index study should be a routine laboratory investigation in cases with GBM.

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