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Lower Plasma Amyloid Beta - 42 Levels Associated With Worse Survival in Patients With Glioma

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Abstract. *Background/Aim: Glioma is often refractory. The accumulation of amyloid beta (Aβ) in the brain is commonly associated with Alzheimer's disease (AD), but there are studies suggesting that Aβ has tumor suppressor potential. The aim of this study was to identify a novel, non-invasive candidate biomarker for histological prediction and prognostic assessment of glioma. Patients and Methods: Serum was prepared from blood samples collected preoperatively from 48 patients with WHO grade II-IV glioma between October 2004 and December 2017 at a single tertiary institution. The concentration of Aβ42 was measured using the SMCxPRO immunoassay (Merck). The clinical and histological characteristics of the patients, including molecular subtypes, were reviewed. Results: The mean age of the patients was 52.2±12.5 years. The mean value of serum Aβ42 concentration was 7.6±7.8 pg/ml in the anaplastic astrocytoma (WHO grade III) group and 6.4±6.5 pg/ml in the glioblastoma multiforme (WHO grade IV) group. The Negative epidermal growth factor receptor (EGFR) expression was associated with higher serum Aβ42 levels (p=0.020). Kaplan–Meier analysis demonstrated that patients with high serum Aβ42 (>11.78 pg/ml) had significantly longer progression-free survival (PFS) (p=0.038) and overall survival (OS) (p=0.018). Conclusion: This study investigated serum Aβ42 levels as a potential biomarker for glioma. The results showed that low serum Aβ42 levels were associated with EGFR expression and poor PFS and OS. Overall, these findings suggest a potential role of Aβ42 as a prognostic marker in astrocytomas.*

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Glioma is a tumor of glial cell origin responsible for 30% of central nervous system neoplasms and 80% of malignant tumors in the brain (1, 2). High-grade glioma exhibits highly aggressive behavior and a dismal prognosis. Glioblastomas (GBMs) account for approximately 40% of all gliomas, and one of the most common genetic changes is epidermal growth factor receptor (EGFR) amplification (3, 4). *EGFR* gene amplification and over-expression are representative prognostic indicators associated with poor outcome in patients with GBM (5-7).

EGFR has demonstrated its role in direct interaction with amyloid beta (Aβ) oligomers in Alzheimer's disease (AD) (8, 9). Several previous studies have shown an inverse correlation between EGFR and Aβ42 expression. Wang *et al*. reported that EGFR levels were severely reduced in aged flies over-expressing Aβ42, leading to neurodegeneration (9). In another study, amyloid precursor protein (APP)/presenilin1 (PS1) dual transgenic mice showing plaque formation and Aβ-induced memory loss recovered memory after treatment with the EGFR inhibitor gefitinib (8). In addition, pan-neuronal expression of Aβ42 is associated with increased glial cell proliferation and reduced EGFR levels in the brain as shown in *in vivo* models (9, 10).

Many previous studies have shown that astrocytes degrade Aβ plaques and internalize Aβ oligomers through restriction enzymes, and their association with amyloid peptides has been reported (11, 12). The accumulation of Aβ in the brain is typically associated with the development of AD, but there are studies suggesting a potential tumor suppressor role for Aβ (13-15). Studies show an inverse association between AD and many types of cancer, including studies showing a 50% lower risk of cancer in people with AD (13, 14). It has also been suggested that high levels of Aβ may indirectly suppress tumor growth by inhibiting neovascularization within tumor masses, blocking cancer-causing viruses, and limiting the availability of trace nutrients needed for cell proliferation by removing free metal ions (13).

In human studies, Aβ has been reported to accumulate in the brain tissue of patients with glioma and to be detectable in cerebrospinal fluid and serum (16, 17). Amyloid precursor protein-derived Aβ42 is known to be transported across the blood-brain barrier in both directions and is mainly supplied from the brain (18, 19). The aim of this study was to evaluate the relationship between serum Aβ42 concentration and prognosis in patients with astrocytoma and to identify a potential non-invasive biomarker for predicting histology and prognosis in glioma.

Patients and Methods

Study population. This was a retrospective cohort study (48 participants in total). Blood samples from patients with glioma who provided informed consent were collected preoperatively at our institution between October 2004 and December 2017. We also collected demographic and tumor-related clinical data, including age at diagnosis, sex, etiology (primary or recurrent), histopathological grade, and tumor subtype according to the World Health Organization (WHO) classification, EGFR expression, GFAP expression, progression-free survival (PFS) and overall survival (OS). This study was approved by the institutional review board of our institution (IRB No. B-1106-129-803).

Immunoassay for amyloid-beta42. Samples were used immediately after collection or stored at –20˚C before being subjected to more than two freeze-thaw cycles prior to use. Reagents from the SMCxPRO kit (Merck KGaA, Darmstadt, Germany) were stored at 4˚C and thawed at room temperature before the experiment.

The blood sample was centrifuged at 13,000 × *g* for 10 min using a microcentrifuge. Only the supernatant was pipetted into a microcentrifuge tube using a pipette and diluted with a standard diluent reagent at a 1:4 ratio. One hundred microliters of standards and a 1:4 diluted sample were added to each well of the assay plate. Anti-Aβ42 antibody-coated beads were sufficiently resuspended for at least 20 min by using a spin rotator or by manual inversion. The anti-Aβ42 antibody coated beads (0.45 ml) were then diluted with 11.55 ml of assay buffer. One hundred microliters of the bead solution were added to each well of the assay plate. The plate was completely sealed and incubated in a microplate shaker at 25˚C and 500 rpm for 2 h. After centrifugation with 20 × detection antibody for 5 min at 14,000 × *g*, 250 μl of the antibody supernatant was mixed with 4,750 μl of assay buffer. The diluted antibody was transferred to a clean tube using a 0.2 μm filter. When incubation of the assay plate was complete, the plate was centrifuged at 1,100 × *g* for one minute, and the seal was opened. The assay plate was placed on a hand-held magnet, and the supernatant was removed with a pipette. After the assay plate was displaced from the hand-held magnet, 20 μl of antibody was added to each well. The plate was covered and placed on a shaker at 25˚C for 30 min.

The plate was replaced on the hand-held magnet, and the supernatant was removed. The beads were washed four times. At the end of washing, 200 μl of 1 × wash buffer was dispensed, after which the plate was displaced from the hand-held magnet. After the plate was sealed, it was agitated at 750 rpm for 90 s, and the supernatant was carefully removed. Ten microliters of buffer D were added to each well, and the plate was placed on a Sphere Mag plate for two min. After 10 μl of the eluate was transferred from the assay plate to the V-bottom plate for reading, the plate was sealed, agitated at 25˚C and 1,500 rpm for one min and centrifuged at 1,100 × *g* for one min at room temperature. The plate was sealed with an aluminium seal and placed in a SMCxPRO (Merck KGaA, Darmstadt, Germany) for analysis. The SMCxPRO was performed as previously described (20).

Tissue acquisition and histopathologic diagnosis. Formalin-fixed paraffin-embedded (FFPE) tissue samples obtained after surgical resection were stained with hematoxylin and eosin (H&E). The diagnosis was confirmed using the World Health Organization (WHO) classification of CNS tumors, 4th edition, 2016.

Immunohistochemistry (IHC) staining was performed on a single representative sample block with specific histomorphological features. The following primary antibodies were used: EGFR (mouse monoclonal antibody, Dako, Camarillo, CA, USA), and GFAP (rabbit polyclonal antibody, Dako). The antigen-antibody reaction was visualized using the Dako REAL EnVision Detection System (Dako, Glostrup, Denmark) and the sections were counterstained with Mayer's hematoxylin. Compared to the negative control group without antibodies, tumor cells were classified and scored as positive if they showed moderate to strong cytoplasmic and/or membranous positivity.

Statistical analyses. Comparisons between groups were performed with a non-parametric Mann–Whitney test. All *p*-values were two-tailed, and the level of significance was set at $p<0.05$.

Survival curves were calculated using Kaplan–Meier estimates and compared using the log-rank test. In the Kaplan–Meier analysis, the upper or lower threshold of serum Aβ42 concentration was 11.776 pg/ml, the optimal cut-off value obtained from the receiver operating characteristic (ROC) curve. ROC curve analysis was performed to define optimal cut-off values of Aβ42 concentration to classify astrocytoma and glioblastoma multiforme.

All data were analyzed using the R statistical package (version 4.0.2) (Foundation for Statistical Computing, Vienna, Austria) and visualized using GraphPad Prism 9 software (GraphPad, San Diego, CA, USA).

Results

Demographics and clinical characteristics of the patients. A total of 48 patients were included in the final analysis: 41 cases of glioblastoma multiforme (WHO grade IV), 5 cases of anaplastic astrocytoma (WHO grade III), and 1 case with diffuse astrocytoma (WHO grade II) (summarized in Table I).

Table I. *Demographic and clinical characteristics of the patients with WHO grade of astrocytoma.*

	WHO grade			
	All	II[1]	III[2]	IV[3]
No. of patients	48	1 (2.0%)	6 (12.5%)	41 (65.1%)
Age in years (mean±SD)	55.2 (±12.5)	50.0 (±0.0)	45.5 (±10.1)	56.7 (±12.3)
Sex				
Male	30 (62.5%)	0	4	26
Female	18 (37.5%)	1	2	15
Immuno-markers				
Amyloid beta 42 (mean±SD, pg/ml)	6.7 (±6.6)	13.6 (±0.0)	7.6 (±7.8)	6.4 (±6.5)
EGFR (No. of positive cases)	40 (83.3%)	1	5	34
GFAP (No. of positive cases)	48 (100%)	1	6	41

[1]Grade II subtypes (Diffuse astrocytoma, n=1), [2]Grade III subtypes (Anaplastic astrocytoma, n=6), [3]Grade IV subtypes (Glioblastoma multiforme, n=41).

The mean (±SD) age of the patients was 52.2±12.5 years. The mean serum concentration of Aβ42 was 6.7±6.6 pg/ml. The positive EGFR expression rate was 83.3% (40/48), while eight patients were negative. All 48 patients were GFAP positive.

Association between serum Aβ42 concentration and astrocytoma progression. The serum concentration of Aβ42 was 13.6 pg/ml in the diffuse astrocytoma (WHO grade II) group. The mean value of serum Aβ42 concentration was 7.6±7.8 pg/ml in the anaplastic astrocytoma (WHO grade III) group and 6.4±6.5 pg/ml in the glioblastoma multiforme (WHO grade IV) group (Table I). The serum concentration of Aβ42 gradually decreased with the progression of astrocytoma to a higher tumor grade.

The mean value of serum Aβ42 concentration was higher in the astrocytoma group (diffuse astrocytoma and anaplastic astrocytoma) than that in the glioblastoma multiforme group, but there was no significant difference between the two groups (Figure 1).

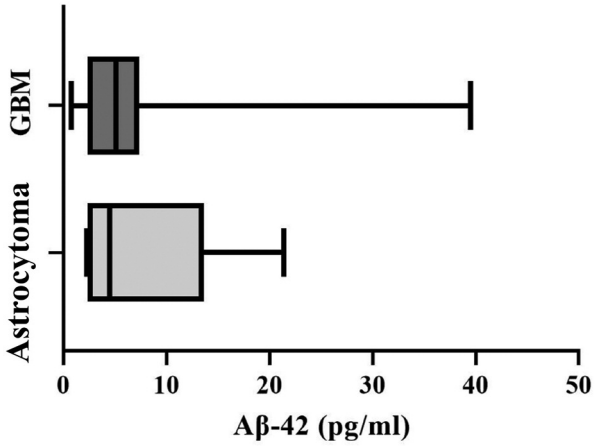

Figure 1. *Comparison of serum Aβ42 concentrations between astrocytoma and glioblastoma multiforme (GBM) groups. Box plots of Aβ42 concentrations are expressed as mean±SD.*

Association between serum Aβ42 concentration and EGFR expression. We analyzed the association between serum Aβ42 concentration and EGFR expression in the astrocytoma and glioblastoma multiforme groups (Figure 2). The median serum Aβ42 concentration was 8.84 pg/ml in the EGFR-negative group and 4.34 pg/ml in the EGFR-positive group (Figure 2A) (p=0.020). In a separate analysis of patients with glioblastoma (n=41), the median serum Aβ42 concentration was 6.78 pg/ml in the EGFR-negative and 4.16 pg/ml in the EGFR-positive expression group (Figure 2B) (p=0.037). Serum Aβ42 levels were significantly higher in the EGFR-negative expression group than those in the EGFR-positive expression group.

Progression-free survival and overall survival based on serum Aβ42 level. Kaplan–Meier analysis showed that the serum Aβ42 levels were associated with progression-free survival and overall survival (Figure 3). The ROC curve determined optimal cut-off values of Aβ42 concentration to classify astrocytoma and glioblastoma multiforme and the value was 11.78 pg/ml (AUC=0.58, sensitivity=92.7%, specificity=42.9%) in all study participants (n=48).

Kaplan–Meier analysis demonstrated that patients with high serum Aβ42 (>11.78 pg/ml) had significantly longer PFS (p=0.038) and OS (p=0.018) (Figure 3). The mean and median PFS of the high Aβ42 group were 28.3±21.3 and 24.8 months, respectively, whereas those of the low Aβ42 group were 20.5±21.3 and 11.0 months, respectively (Figure 3A). The mean and median OS of the high Aβ42 group were 39.5±22.4 and 35.0 months, respectively, whereas those of the low Aβ42 group were 29.3±28.8 and 23.0 months, respectively (Figure 3B).

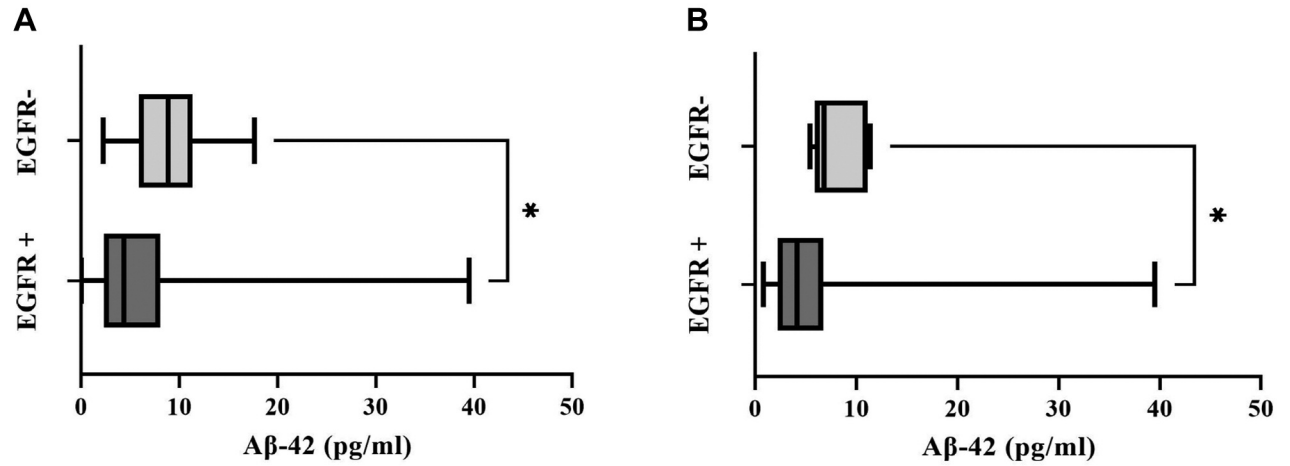

Figure 2. *Comparison of serum concentrations of Aβ42 between the EGFR positive and EGFR negative groups. (A) Data are from patients with diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme (n=48). (B) Data are from patients with glioblastoma multiforme (n=41). Significance of differences between groups was determined using the non-parametric Mann–Whitney test. Values are expressed as mean±SD, *p<0.05.*

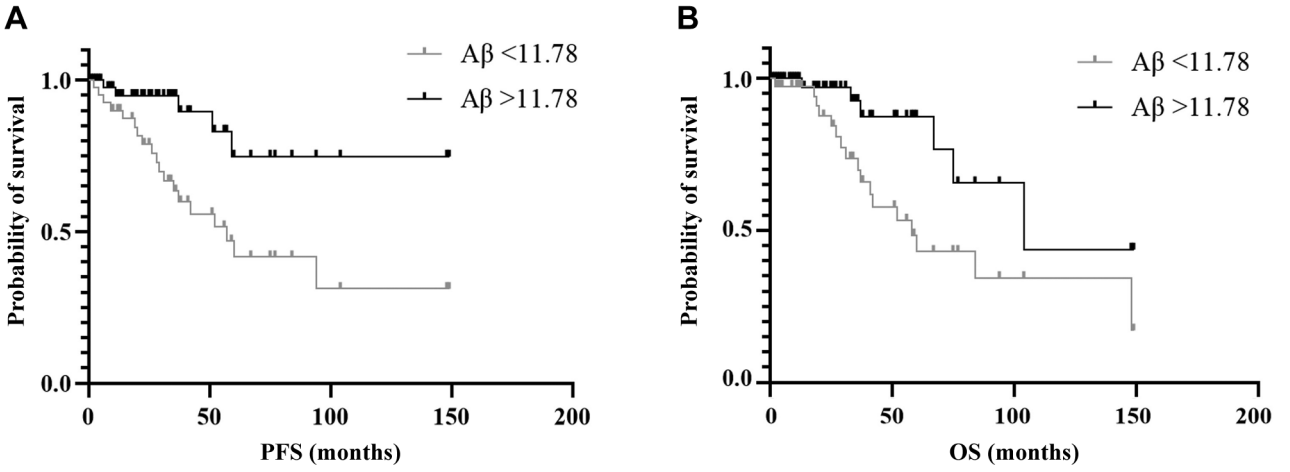

Figure 3. *Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) of patients with astrocytoma based on serum Aβ42 levels. Survival analysis using Kaplan–Meier curves and log-rank (Mantel–Cox) test. Kaplan–Meier curves show PFS (A) and OS (B) of patients with high and low Aβ42 levels according to the cut-off Aβ42 level of 11.776 (PFS, p=0.0038; OS, p=0.0180).*

Discussion

This study investigated serum Aβ42 levels as a candidate serum biomarker for glioma. The results demonstrated that low serum Aβ42 levels were associated with wild-type EGFR expression, and poor PFS and OS.

GFAP is known as a classical marker of astrocytoma but may not be a direct indicator of glial differentiation and malignant phenotype due to its heterogeneous expression (21). In our study, GFAP expression was confirmed in all patients (Table I).

Astrocytomas are subdivided into astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and glioblastoma multiforme (WHO grade IV) based on biological behavior and malignancy. Studies have reported that high-grade astrocytoma is highly associated with *EGFR* amplification and over-expression (22). EGFR is altered in several ways in glioma, including over-expression, amplification, and deletion. Alterations in EGFR promote cell proliferation, neurogenesis, angiogenesis, and invasion. Previous studies have also shown that neuronal expression of EGFR reduces the formation of Aβ42 in the brain and induces cell proliferation (9, 10).

Astrocytes are also known to contribute to Aβ degradation by expressing several proteolytic enzymes involved in Aβ cleavage and may also influence Aβ homeostasis (11, 12).

In addition, previous studies have reported that EGFR is directly related to Aβ peptide formation. A reduction in EGFR and Aβ plaque formation is observed in elderly patients with AD, whereas Aβ plaque formation acts as a tumor suppressor in cancer patients. Our study also confirmed that serum Aβ42 levels were significantly lower in the EGFR-positive expression group than those in the EGFR-negative group (Figure 2).

In previous studies, Aβ has been shown to play an important role in maintaining physiological vascularization at appropriate levels, but there are studies in patients with AD showing that as Aβ level increases, it excessively promotes abnormal angiogenesis with inappropriate blood vessel formation, leading to vascular dysfunction (23-25). In contrast to the association of Aβ accumulation in AD patients, some studies have proposed a potential tumor suppressor role for Aβ, as evidenced by a decrease in cancer incidence in individuals with high Aβ levels or AD (13-15). Previous studies have shown that transplantation of gliomas into AD transgenic mice over-expressing Aβ reduces tumor growth and that Aβ inhibits renal angiogenesis (26). It has also been shown to suppress tumor growth indirectly by blocking cancer-causing viruses or by removing free metal ions to limit the availability of micronutrients needed for cell proliferation (13). It is possible that lowering Aβ could increase the rate of tumor proliferation (15, 27), and our study also showed poor PFS and OS outcomes in groups with low serum Aβ concentrations (Figure 3).

In summary, the concentration of Aβ42 was lower in the group of patients with glioblastoma than that in the group of patients with lower grade astrocytoma (WHO grade II, III) (Figure 1). The low Aβ42 group had a lower survival rate than the high Aβ42 group. This finding is similar to previous studies suggesting that Aβ has tumor suppressor potential. These results suggest that Aβ42 has a potential role as a prognostic marker in astrocytoma.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

Authors' Contributions

Conception and design: K.-S.A. and C.-Y.K.; Acquisition of data: All Authors; Analysis and interpretation of data: K.H., K.S. and M.N.; Drafting and revision of the manuscript: K.H., K.S. and M.N.; Final approval: All Authors.

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