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Diffusion Kurtosis Imaging Reflects Glial Fibrillary Acidic Protein (GFAP), Topo IIα, and O⁶-Methylguanine-DNA Methyltransferase (MGMT) Expression in Astrocytomas

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Astrocytomas are the most common primary brain neoplasms. Biological indicators of astrocytomas can reflect its biological characteristics. The aim of this study was to assess the expression of the pathological glial fibrillary acidic protein (GFAP) Topo IIα and O⁶-methylguanine-DNA methyltransferase (MGMT) in astrocytomas using magnetic resonance (MR) diffusion kurtosis imaging (DKI) to evaluate the biological characteristics of astrocytomas.

Material/Methods: Sixty-six patients with pathologically proven astrocytomas were enrolled in this study. All patients underwent conventional MRI head scanning, DKI scanning, and enhanced scanning under the same conditions. Spearman's rank correlation analysis and Bonferroni correction were used to compare the values of DKI and the expression levels of GFAP, Topo IIα, and MGMT between the 2 groups.

Results: Mean kurtosis (MK) values were negatively correlated with the expression of GFAP (r=–0.836; P=0.03). However, these were positively correlated with the expression of Topo IIα (r=0.896; P=0.01). Moreover, fractional anisotropy (FA) values were not correlated with the expression of GFAP (r=0.366; P=0.05), Topo IIα (r=–0.562; P=0.05), or MGMT (r=–0.153; P=0.10).

Conclusions: MK was significantly associated with the expression of GFAP and Topo IIα. To a certain extent, applying DKI may show the biological behavior of tumor cell differentiation, proliferation activity, invasion, and metastasis, and guide individual treatment.

MeSH Keywords: Astrocytoma • Diffusion Magnetic Resonance Imaging • DNA Topoisomerases, Type II • Glial Fibrillary Acidic Protein • O(6)-Methylguanine-DNA Methyltransferase

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Background

Astrocytomas are the most common adult primary neuroepithelial tumor. Factors affecting the biological behavior of astrocytomas are very complex. Although routine pathological diagnosis and classification are important in assessing the effect of clinical treatment, it does not fully reflect the biological behavior of these tumors [1]. To better assess the biological behavior of this tumor, it is necessary to reveal the development of astrocytomas at the molecular biological level, and appropriate treatment measures can be used to achieve targeted therapy. Recent studies have shown that glial fibrillary acidic protein (GFAP) [2], DNA topoisomerase IIα (Topo IIα) [3], and O6-methylguanine-DNA-methyltransferase (MGMT) [4] can reflect the biological behavior of a tumor.

Magnetic resonance imaging (MRI) is commonly used in noninvasive clinical examination and in of grading astrocytomas. Fractional anisotropy (FA) and mean diffusivity (MD) obtained from diffusion tensor imaging (DTI) have been used to grade gliomas. However, FA and MD have limitations in accurately evaluating GFAP, Topo IIα, and MGMT.

New technologies, such as diffusion kurtosis imaging (DKI), can provide information on the pathophysiology of cancer. Defining the relationship between DKI parameter and the corresponding expression of GFAP, Topo IIα, and MGMT can provide more abundant imaging information to better assess the biological behavior of tumors and to guide cancer diagnosis and treatment.

DKI has been used to measure the non-Gaussian nature of water diffusion, which can reveal a more complex microstructure in both normal and pathological tissues compared to DTI. Previous studies have demonstrated that there was a significant difference in mean kurtosis (MK) value between high- and low-grade astrocytomas [5]. However, to the best of our knowledge, no comparison of different diffusion imaging approaches for assessing the expression of GFAP, Topo IIα, and MGMT in astrocytomas has been investigated to date.

The aim of this study was to quantitatively compare the potential of parameters obtained from DTI and DKI in assessing the expression of GFAP, Topo IIα, and MGMT in astrocytomas.

Material and Methods

Study

Sixty-six patients with pathologically proven astrocytomas (22 males and 44 females; age range: 22–71 years old, mean age: 42 years old) in the First Hospital of Shanxi Medical School from March 2012 to September 2014 were enrolled in the study. All patients underwent preoperative conventional magnetic resonance imaging (MRI) head scans, DKI scans, and enhanced scans under the same conditions. Then, these patients underwent surgery 2 weeks later. Immunohistochemistry results for GFAP, Topo IIα, and MGMT were available.

All pathological specimens obtained by experienced experts were in accordance with the 2007 World Health Organization (WHO) neuropathological classification criteria for the diagnosis of central nervous system tumors. Among these patients, 34 were assigned to the high-grade astrocytomas group (WHO III–IV grade) and 32 patients were assigned in the low-grade astrocytomas group (WHO I-II grade). This study was approved by the local Ethics Committee and informed consent was obtained from all patients.

Image acquisition and quantitative imaging analysis

A GE 3.0T MRI and a head and neck joint eight-channel phased-array coil were used for scanning. Conventional MRI head scans, DKI scans, and enhanced scans were obtained under the same conditions. T1-weighted image (WI) fluid-attenuated inversion recovery (FLAIR) sequence parameters were as follows: TR=1686 ms, TE=24.2 ms, thickness=6.0 mm, and FOV=24 cm. T2WI sequence parameters were as follows: TR=6600 ms, TE=107.2 ms, thickness=6.0 mm, and FOV=24 cm. T2WI FLAIR sequence parameters were as follows: TR=8000 ms, TE=126.8 ms, thickness=6.0 mm, and FOV=24 cm. Diffusion-weighted imaging (DWI) with echo-planar imaging (EPI) scan parameters were as follows: TR=6550 ms, TE=116 ms, FOV=24 cm, thickness=6.0 mm, 15 diffusion-sensitive gradient fields, and b values=0, 1000 s/mm^2. DKI with EPI sequence scan parameters were as follows: TR=6550 ms, TE=116 ms, FOV=24 cm, thickness=6.0 mm, 30 diffusion-sensitive gradient fields, and b values=0, 1000 s/mm^2 and 2000 s/mm^2. T1WI enhanced scan parameters were as follows: TR=2002.20 ms, TE=24.20 ms, thickness, 6.0 mm, and FOV=24 cm.

Images were transferred to a workstation (Advantage Workstation 4.4, GE Medical System) for processing and then were evaluated by 2 senior doctors. According to conventional MRI results, an area of abnormal strengthening lesions (avoiding cystic degeneration, necrosis, large blood vessels, bleeding, and calcification for parameter measurement) was identified as the region of interest (ROI) of the tumor. As ROIs changes from 25 to 50 mm^2 (average size is 36 mm^2), we used Cholesky decomposition to calculate FA and MK values using a linear least-square fitting algorithm with constraint on ROIs diffusion tensor.

Statistical analysis

SPSS version 16.0 statistical software was used to process all statistical data. Measurement data are presented as $\bar{\chi}\pm$

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Table 1. DKI parameter values ($\bar{\chi}$±S) between high-grade and low-grade astrocytomas group.

Parameters	n	FA	MK
Low-grade group	32	0.23±0.09	0.48±0.09
High-grade group	34	0.15±0.06	0.68±0.16
P		0.331	0.005*

Table 2. GFAP, Topo-IIα, and MGMT expression between groups ($\bar{\chi}$±S).

Parameters	n	GFAP	Topo-IIα	MGMT
Low-grade group	32	0.19±0.03	15.29±5.53	0.14±0.10
High-grade group	34	0.10±0.03	42.10±12.3	0.16±0.09
P		0.001*	0.000*	0.679

standard deviation (SD). A two-sample Bonferroni correction was performed to compare parameter values between the 2 groups in terms of DKI and GFAP, Topo IIα, and MGMT expression level differences. Spearman rank correlation analysis was conducted to analyze DKI parameter values correlated with GFAP, Topo IIα, and MGMT expression. $P<0.05$ was considered statistically significant.

Results

Diffusion kurtosis imaging parameter values in astrocytomas

The MK values were significantly higher in the high-grade astrocytomas group than in the low-grade astrocytomas group ($P<0.05$). Furthermore, the difference in FA values between the high- and low-grade astrocytomas groups was not statistically significant ($P=0.331$, Table 1).

GFAP, Topo IIα and MGMT expression analysis in astrocytomas

The expression of GFAP was positive or strongly positive in the low-grade astrocytomas group, but this was weakly positive or there was no expression in the high-grade astrocytomas group. Furthermore, the expression of GFAP between the high- and low-grade astrocytomas groups was significantly different ($P<0.05$). The expression of Topo IIα was weakly positive or there was no expression in the low-grade astrocytomas group, but was positive or strongly positive in the high-grade astrocytomas group, and the expression of Topo IIα between the high- and low-grade astrocytomas groups was significantly different ($P<0.05$). Moreover, the difference in the expression of MGMT between the high- and low-grade astrocytomas groups was not statistically significant ($P=0.679$, Table 2).

Correlation between DKI parameter values and the expression of GFAP, Topo IIα and MGMT in astrocytomas

Spearman rank correlation analysis revealed that the MK value was negatively correlated ($r=-0.836$, $P=0.03$) with the expression of GFAP, was positively correlated ($r=0.896$, $P=0.01$) with the expression of Topo IIα, and was not linearly correlated with the expression of MGMT ($r=0.362$, $P=0.05$). Furthermore, there was no linear correlation between FA values and the expression of GFAP ($r=0.366$, $P=0.05$), Topo IIα ($r=-0.562$; $P=0.05$), and MGMT ($r=-0.153$, $P=0.10$) (Figures 1–4).

Discussion

With the rapid development of some new functional MRI techniques in recent years, we can not only observe the morphology and structure of brain tumors better, but also receive more valuable information. 1H-MRS can provide information on the chemical composition of metabolites in living organisms [6]. PWI can assess the perfusion state of tissue microcirculation [7]. DKI, an extension of DTI technology, is a new MRI method for describing the diffusion of non-Gaussian water molecules in tissues. Compared with DTI, 1H-MRS, and PWI, DKI is more suitable for demonstrating changes in the microstructure of organisms. MK, the parameter of DKI, is more sensitive than PWI and MRS in assessing heterogeneous diffusion of glioma, and has important clinical significance in evaluating the pathological grading and molecular biological changes of glioma [8].

Role of DKI in brain astrocytomas grading

DKI has the potential to measure the non-Gaussian diffusion in biological tissues [9]. Based on the results of the present study, there was no significant difference in FA value between high- and low-grade astrocytomas, while there was

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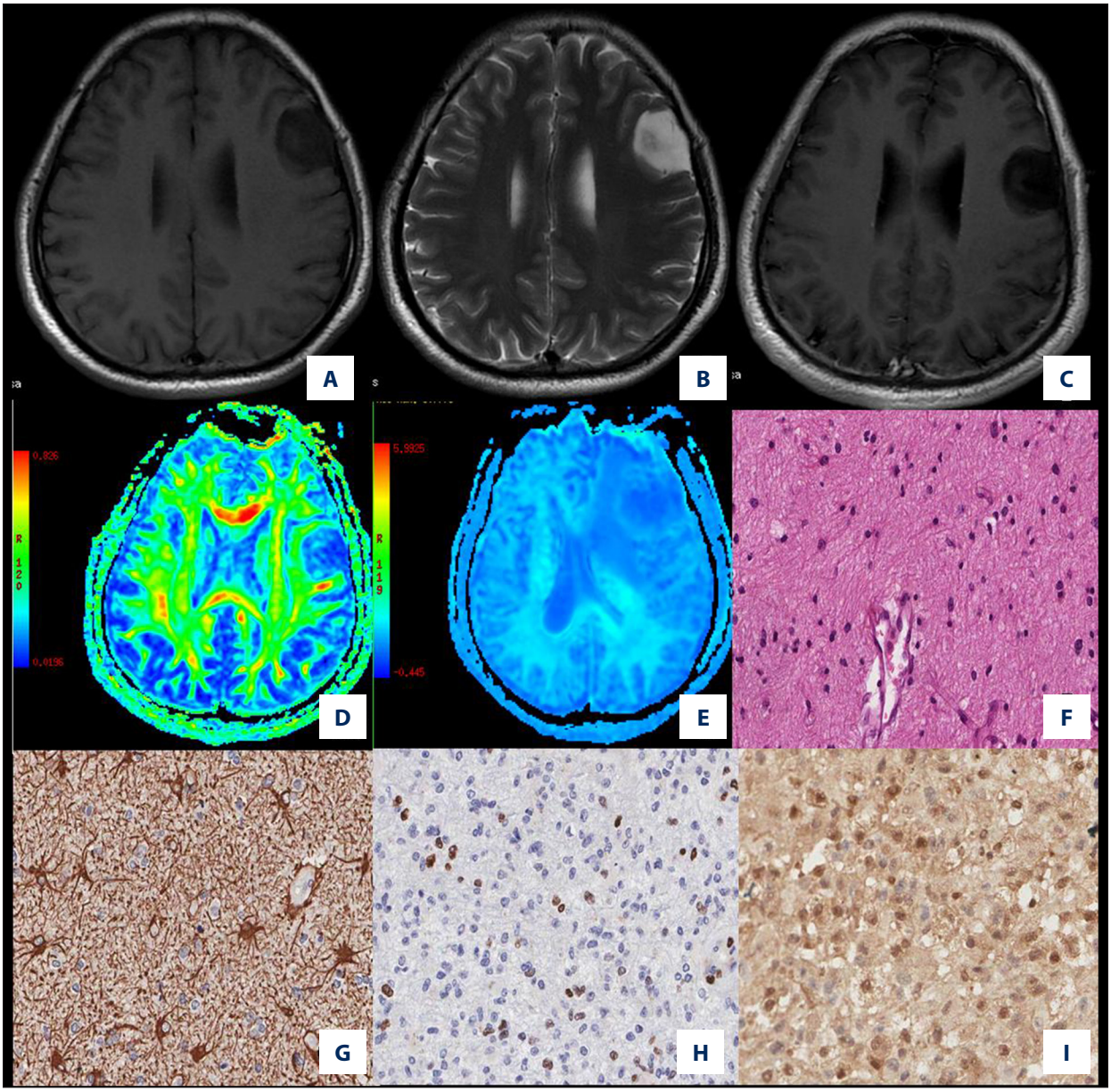

Figure 1. Left frontal astrocytoma (WHO I level), case 1, male patient, 32 years old: (**A**) the lesion appeared hypointense on T1WI; (**B**) the lesion appeared hyperintense on T2WI; (**C**) none of the lesions were significantly enhanced on the enhanced T1WI; (**D**) FA figure; (**E**) MK figure; (**F**) pathology grade I astrocytoma (hematoxylin and eosin, ×400); (**G**) GFAP staining cytoplasm and cell processes with rich brown stained particles; (**H**) Topo IIα staining shows rare nuclei stained brown particles; (**I**) MGMT stained cytoplasm and nucleus with rich brown dye particles.

a significant difference in MK value between high- and low-grade astrocytomas.

MK is the true state of the diffusion of water molecules. Its size depends on the degree of tissue cell structure. The more complicated the structure of water molecules and non-Gaussian distribution restricted diffusion, the higher the MK value is [10]. The degree of tumor differentiation in brain astrocytomas malignancy, invasion, and metastasis are associated with the tissue structure [11,12]. The tumor may make brain tissue lose structural integrity, and tumor tissue cells can increase the internal and external diffusion barrier and restrict the movement of water molecules [13,14]. In the present study, the FA value was not significantly different between the high- and low-grade astrocytomas groups. This shows that the directional diffusion of water molecules in brain astrocytomas was not significantly different, suggesting infiltrative tumor growth, white matter irregular fiber structure damage, normal white

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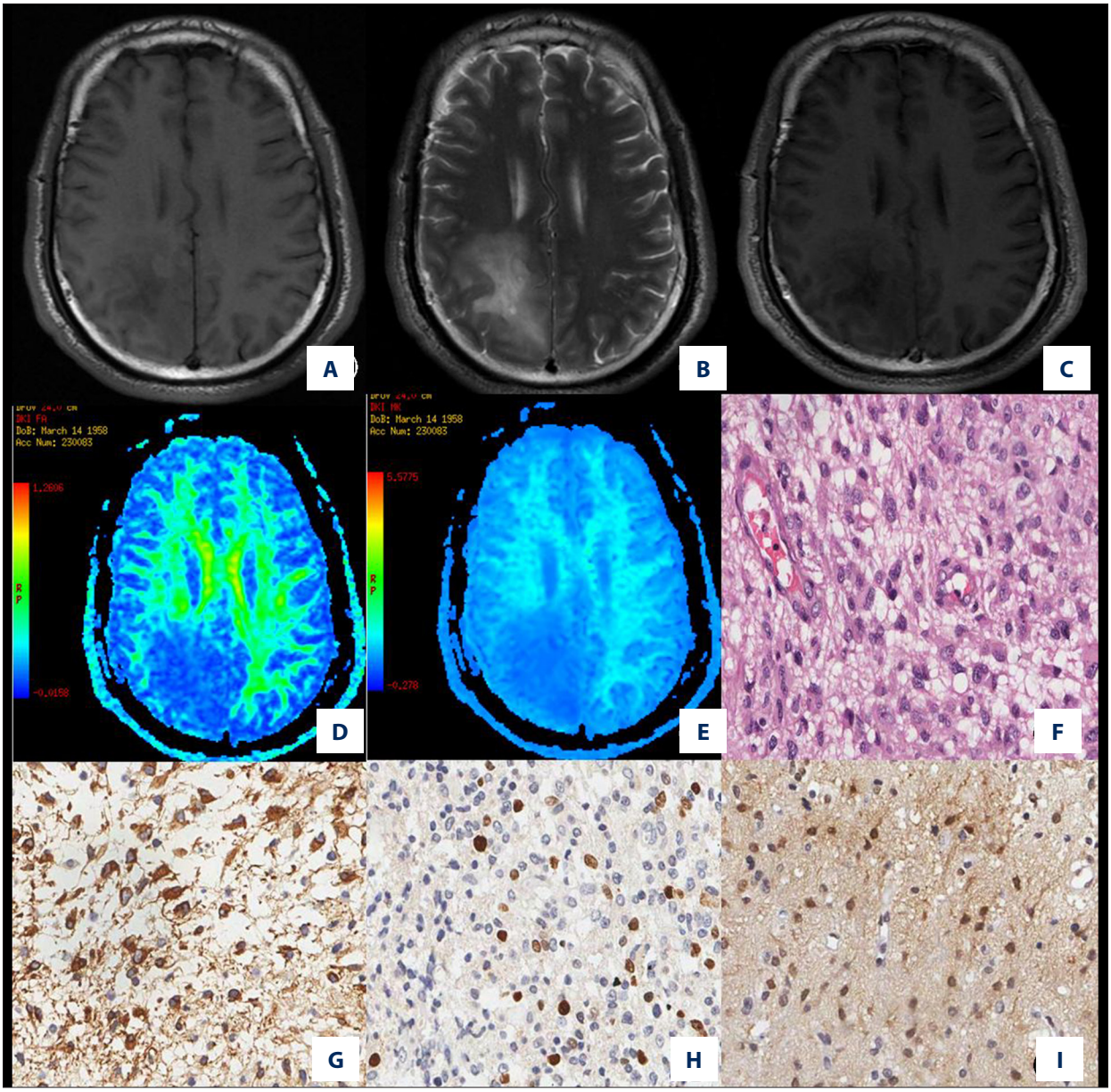

Figure 2. On the left parietal lobe astrocytoma (WHO II level), case 2, male patient, 45 years old: (**A**) the lesion appeared hypointense on T1WI; (**B**) the lesion appeared hyperintense on T2WI; (**C**) none of the lesions were significantly enhanced on the enhanced T1WI; (**D**) FA figure; (**E**) MK figure; (**F**) pathology results for grade II astrocytoma (hematoxylin and eosin, ×400); (**G**) GFAP staining cytoplasm and cell processes with visible brown-stained particles; (**H**) Topo IIα stained nuclei with visible brown dye particles; (**I**) MGMT stained cytoplasm and nuclei staining had visible brown particles.

matter fiber tissues and tumor tissues were mixed, and only part of the water molecule diffusion was not restricted by normal myelinated nerve fibers. Therefore, there was no significant difference in FA values between these 2 groups. MK values were significantly higher in the high-grade astrocytomas group than that in the low-grade astrocytomas group, suggesting the presence of more complex tissue structures, atypical cells, and a polymorphonuclear cell nucleus in high-grade astrocytomas.

The clinical significance of the difference between DKI and GFAP expression

GFAP is an intermediate filament cytoskeletal protein that is specifically expressed in star-shaped cells and determines the function and structure of astrocytes [15], which are astrocytomas derived from astrocytes. Karsy [16] and Guichet [17] reported that the GFAP expression status of the biological behavior of the prognosis of astrocytomas and patients are

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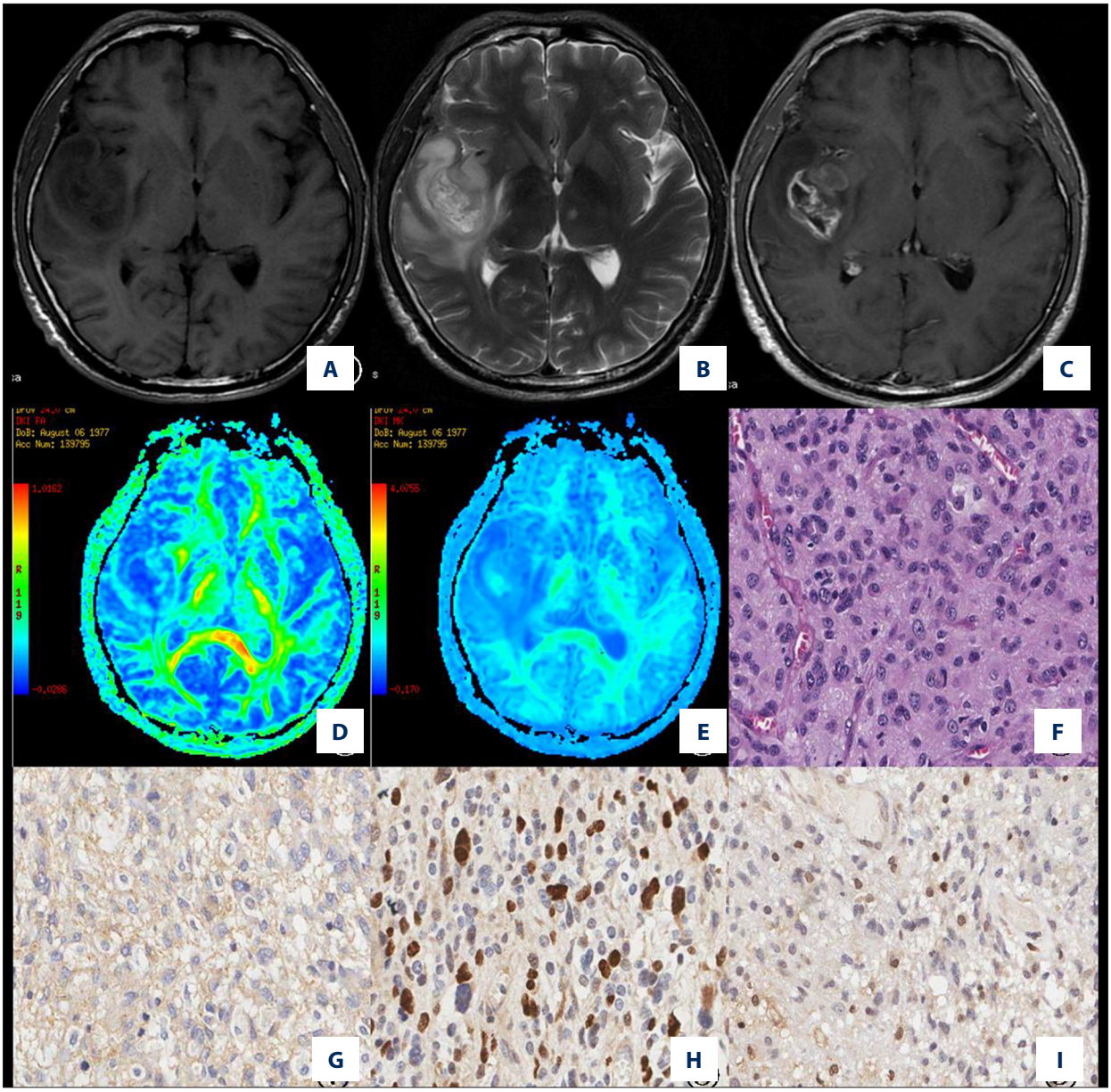

Figure 3. Right temporal lobe astrocytoma (WHO grade III), case 3, male patient, 55 years old: (**A**) the lesion appeared hypointense on T1WI; (**B**) the lesion appeared hyperintense on T2WI; (**C**) T1WI revealed that the lesion was significantly enhanced with an irregular ring enhancement; (**D**) FA figure; (**E**) MK figure; (**F**) pathology results for grade III astrocytoma (hematoxylin and eosin, ×400); (**G**) GFAP stained cytoplasm and cell processes had visible brown-stained particles; (**H**) Topo IIα stained nuclei with rich brown dye particles; (**I**) MGMT stained cytoplasm and nuclei staining with visible brown particles.

closely correlated. The present study shows that the pathology of high-grade brain astrocytomas is related to the low expression of GFAP, immature cells, disordered tissue structure, and poor prognosis. This confirms that GFAP is important for the grading of astrocytomas. A missing GFAP expression can induce structural changes in the star cytoskeleton, cause the loss of important intercellular interconnections, and allow the tumor cell to easily infiltrate into the adjacent tissue, leading to the loss of structural integrity of the brain tissue and limitations of the movement of water molecules into and out of tumor tissue cells.

DKI dispersion degree in different grades of brain astrocytomas tissue changes in water molecules can be used to evaluate tumor cell infiltration depth, differentiation, the degree of malignancy, and other biological behaviors. The present study shows that GFAP expression in brain astrocytomas is associated with MK. Furthermore, due to the differentiation of the

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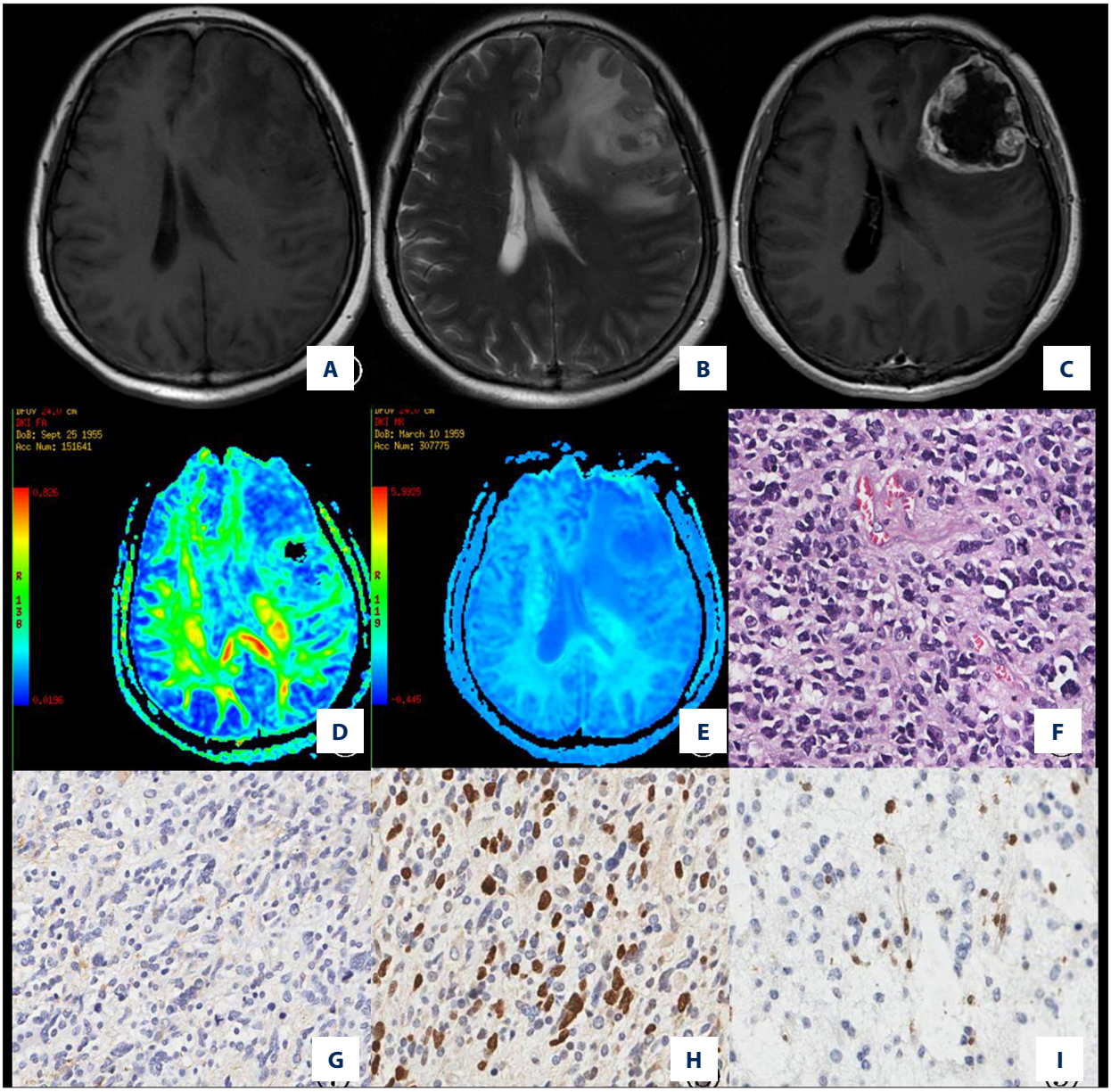

Figure 4. On the left frontal astrocytoma (WHO IV grade), case 4, female patient, 62 years old: (**A**) the lesion appeared hypointense on T1WI; (**B**) the lesion appeared hyperintense on T2WI; (**C**) the enhanced T1WI revealed that the lesions presented a rosette-like enhancement; (**D**) FA figure; (**E**) MK figure; (**F**) pathological results of IV grade astrocytoma (hematoxylin and eosin, ×400); (**G**) GFAP staining cytoplasm and cell processes presented rare brown stain particles; (**H**) Topo IIα staining had visible rich nuclei stained brown particles; (**I**) MGMT stained cytoplasm and nucleus had rare brown-stained granules.

tumor cells, and the low malignancy and tight connection among tissue cells, tumor cell growth will easily infiltrate into the complex tissue structure to a lesser extent. In addition, if the water diffusion barrier is relatively less constrained, the MK value will be small, low-grade tumor pathology will be observed, and the prognosis will be good. The GFAP expression in astrocytomas was not correlated with the FA value because GFAP expression may be decreased or absent, causing skeletal tissue structure change and the interaction of weakened cells, and allowing tumor cells to easily infiltrate into the adjacent tissue and permitting the normal white matter fiber tissue to mix with tumor tissues. The white matter fiber structure is irregularly damaged, only some of the water molecules diffuse, and there is loss of normal myelinated nerve fiber constraints. Therefore, FA values and GFAP were not linearly correlated. For MK values, the DKI parameter value is reflected with the GFAP expression grades of brain tumor astrocytomas.

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The clinical significance of DKI and Topo IIα expression

Topo IIα, an important nuclear enzyme, is required for the transcription of DNA replication, is critical in many chemotherapeutic drug target enzymes, and is an important prognostic biological marker of brain astrocytomas. Studies have also shown that Topo IIα expression is correlated with M, S, and G2 phases of the cell activity cycle, and it can better reflect tumor cell proliferation [18]. In the present study, the Topo IIα expression of astrocytomas was significantly higher in the high-grade astrocytomas group than in the low-grade astrocytomas group. This confirms that Topo IIα expression in the brain is important for the tumor grading of astrocytomas. As the tumor pathological grade increases, Topo IIα expression significantly increases, the proliferation of malignant cells significantly increases, and the prognosis becomes worse. If there are higher degrees of malignancy, more tumor tissues are dense, more nuclear atypia are found, richer tumor blood vessels are present, and more severe necrotic tissues are observed, the tumor tissue will have a more diffused barrier, the microscopic structure would be more complex, the limited extent of diffusion would be more pronounced, and the water molecules Gaussian diffusion displacement deviation will be greater. DKI describes the non-Gaussian diffusion displacement of the body's water molecules in order to quantify the diffusion of water molecules that are not homogeneous and to quantify the limited extent of its diffusion. The present study found that MK values were significantly correlated with Topo IIα expression grades. Topo IIα expression was found in high-grade tumors, suggesting that the proliferation of malignant tumor cells is quicker, the tissue is denser, and the movement of water molecules is more obviously limited, resulting in the significant increase in MK parameter values in tissues. The expression of Topo IIα in astrocytomas was not correlated with FA values, which may be due to the infiltrative growth of brain astrocytomas, the mixing of normal white matter fiber tissue and tumor tissue, the irregular fiber structure of white matter damage, the loss of normal myelinated nerve fiber constraint in part of the water molecular diffusion, the insignificant difference in FA values among tumors, and the absence of the significant linear correlation of FA values with Topo IIα. Therefore, MK values and DKI parameters can reflect the Topo IIα expression grade in astrocytomas.

The clinical significance of DKI and MGMT expression

Temozolomide is a chemotherapeutic drug that can be used to treat brain astrocytomas [19]. MGMT can repair DNA damage through reversing temozolomide alkylation, and the reduced MGMT expression in brain astrocytomas during temozolomide chemotherapy can be an important indicator for the sensitivity of temozolomide chemotherapy. Studies conducted by Li [20] and Lan [21], as well as other studies on the association of different pathological grades of glioma with the expression of MGMT, have reached the opposite conclusion. The present study revealed that the overall expression level of MGMT was higher in the high-grade astrocytomas group than in the low-grade astrocytomas group, suggesting differences in the overall expression of MGMT temozolomide tolerance and prognosis between high-grade and low-grade astrocytomas. However, the expression of MGMT between the high-grade and low-grade astrocytomas groups was not statistically significant. This implies that the differences in MGMT expression among individuals are significant, and further studies are needed. Recently, Li [22] determined the expression of MGMT in 42 patients with glioblastoma tumors during surgery using immunohistochemistry staining with T2WI MRI. The results revealed edema and that the MGMT expression level was associated with edema. Moon [23] used DTI and DSC-PWI to analyze MGMT and MRI correlation for the multiparameter analysis of high-grade glioma. Results revealed that MGMT expression was negatively correlated with the apparent diffusion coefficient (ADC) value and that MGMT expression and FA value revealed a significant positive correlation. DKI evolved from the evolution of DTI technology. It can be used to describe the non-Gaussian diffusion of the water molecule in tissues, quantify the deviation between the true displacement and Gaussian diffusion at an ideal state of water molecules, and DTI can better reflect tissue microstructure changes. However, the different results from the study conducted by Moon show that FA and MK values have no linear correlation with MGMT expression, suggesting that MRI cannot clearly assess the level of significance of MGMT expression. Therefore, further studies are needed.

Conclusions

Our results suggest that MK values can provide more valuable information on the grading of astrocytomas than that provided by FA values. In addition, MK was significantly associated with GFAP and Topo IIα expression. To a certain extent, the application of DKI may reveal the biological behavior of tumor cell differentiation, proliferation activity, invasion, and metastasis, and provide guidance in individual treatments.

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