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Different IDH Mutation and 1p/19q Codeletion Rates between Astrocytoma, Oligodendrocytoma and Mixed Gliomas

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Abstract

Background: The mutations of isocitrate dehydrogenase (IDH-mt) and loss of chromosome 1p and 19q (1p/19q codeleltion) have been used in diagnosis of gliomas, especially in identification of oligodendrocytoma. We have performed and analyzed genetic detections with 3 types of gliomas diagnosed by morphological methods.

Methods: The DNA extracted from tumor tissues of 136 patients with astrocytoma, oligodendrogliomas and mixed gliomas were subjected to fluorescence PCR capillary electrophoresis for detection of 1p and 19q codeletion and DNA sequencing for IDH mutations. The results were analyzed by SPSS 22.0 software with chi-square test for significant difference ($p<0.05$).

Results: Among 136 patients, 77 cases (56.6%) were histopathologically diagnosed as astrocytoma (AA, WHO), 11 (8.0%) as pure oligodendroglial tumors including both low-grade oligodendrogliomas (OA, WHO) and anaplastic oligodendrogliomas (AOA, WHO), and 48 (35.4%) as mixed glioma with the features of OA and AA in the same tumor tissue. The genetic detections have shown that 39 cases (28.7%) were with IDH mutations (37 *IDH1*-mt p.R132H and 2 *IDH2*-mt), and 47 (34.6%) with 1p/19q co-deletion. The significant differences of the IDH mt ($p=0.008$) and 1p/19q codeletion ($p=0.011$) were between 3 pathological types of astrocytoma, oligodendrogliomas and mixed glioms ($p=0.008$). In three glioma types, the rate of 1p/19q co-deletion was highest in the group of oligodendrogliomas ($p=0.040$). In 11 patients who were histopathologically diagnosed as oligodendroglioma, only 5 cases meet the WHO criterion that requires the presence of both 1p/19q codeletion and *IDH1*-mt or *IDH2*-mt.

Conclusion: The rate of IDH mutations and 1p/19q codeletion is significantly different in three groups of gliomas, and highest in oligodendrogliomas. Some cases of oligodendrogliomas with only IDH mutation but without 1p/19q codeletion. Therefore, the genetic detections should be complemented for diagnosis of gliomas.

Keywords: IDH mutations; 1p/19q Codeletion; Gliomas; Oligodendrocytoma

Background

As a most common primary tumor of the central nervous system, glioma is about 80% of intracranial malignant tumors [1]. Diagnosis by microscopy, the diffuse grade and gliomas are histologically divided into two subtypes, oligodendroglioma and astrocytoma. In addition, a third mixed category of oligoastrocytoma is used to describe the glioma cases with the morphology of both oligodendroglioma and astrocytoma [2]. In 2016, the molecular genetic parameters were firstly introduced into the diagnosis of glioma in the World Health Organization (WHO) Classification of Tumors of the Central Nervous System [3]. The new WHO brain tumor classification defines different diffuse gliomas primarily according to the presence or absence of isocitrate dehydrogenase 1 or 2 (IDH) mutations (IDH-mt) and combined the complete deletion of both the short arm of chromosome 1 and of the long arm of chromosome 19 (1p/19q co-deletion) [4]. Therefore, the diagnosis of an anaplastic oligodendroglioma requires the presence of both 1p/19q codeletion and *IDH1*-mt or *IDH2*-mt [5].

The *IDH1* gene mutation happens at the 395 nucleotide position, where G is replaced by A, resulting in replacing arginine 132 (132R) by a histidine (c.395G>A resulting in p.R132H [6,7]. Therefore, the *IDH1* mutation has been used as a molecular biomarker that might be valuable in the clinical practice to assess gliomas prognosis [8,9]. In this study, we have used molecularly genetic methods to detect IDH mutations and 1p/19q co-deletion in glioma cases and analyzed the possible associations with morphological parameters.

Materials and Methods

Patients

A total of 136 glioma cases had been recruited. The patients were with the surgical treatment and diagnosis by histological pathology at the Department of Neurosurgery, General Hospital of Shenyang Military Region, Shenyang, China, from April 2012 to December 2017. All patients were first episode, and none of them had previously received radiotherapy and chemotherapy. The study was approved by the Ethics Committee of the hospital. All study objects are informed consent before the detection. The range of glioma grades was from one

to three, based on the morphological criteria in WHO Classification of Tumors of the Central Nervous System [3]. All pathological examinations of tumor tissues were conducted by two nerve pathology specialists.

Detection of 1p/19q co-deletion and IDH mutations

Fresh tumor samples from patients were snap-frozen in liquid nitrogen and immediately stored at –80°C until DNA extraction. For comparative purposes, blood samples from unrelated healthy controls free of brain tumors or other major of CNS tumors were collected. The DNA was extracted from tumor tissues and peripheral blood samples of patients using Qigen DNA FFPE Tissue Kit and Tiangen peripheral blood drawer Kit and used for PCR amplification. Fluorescence PCR capillary electrophoresis was used to detect the loss of chromosome 1p and 19q, and PCR sequencing analysis to determine mutations of IDH gene. The DNA from peripheral blood samples was used as controls. Because 1p36.1-36.3 and 19q13.3 are common missing areas in chromosome 1 and chromosome 19, for primer synthesis, we chose three STR sites from each of them. They are D1S489, D1S548, D1S1592, D19S219, D19S412, PLA2G4C. The fluorescence markers were also carried out during the process of primer synthesis. The PCR products were used to detect 1p/19q co-deletion by electrophoresis and IDH mutations by DNA sequencing.

Statistical analysis

The data in the group is preliminarily described by percentage method, and the comparison of the data between groups is analyzed by SPSS 22.0 software with chi-square test, and $p<0.05$ was considered statistically significant. For the data of theoretical frequency less than 5, Fisher's exact probability method is used to carry out statistics.

Result

Pathological diagnosis

Among 136 patients, 72 were male and 64 were female, and the ratio of male and female was 1.25:1. The age ranged between 5 and 78 years old, with a median of 46.0-years-old. Within all patients, 77 cases (56.6%) were histopathologically diagnosed as astrocytoma (AA, WHO), 11 (8.0%) as pure oligodendroglial tumors including both low-grade oligodendrogliomas (OA, WHO) and anaplastic oligodendrogliomas (AOA, WHO) [10], and 48 (35.4%) as mixed glioma with the features of low-grade oligodendrocytes (OA) and astrocytoma (AA) in the same tumor tissue.

Determination of 1p/19q co-deletion

After capillary electrophoresis finished, we recorded the peak points in different STR locus and compared the results of tumor tissue and peripheral blood. The missing status of STR locus could be decided when the main peak disappeared or reduced more than 50%. Figure 1, B and C, showed the detective consequence of chromosome 1p and 19q in a case of oligodendrocyte. By comparing the signals of the tumor tissue and the peripheral blood sample from the same person, a significant difference could be seen in the peak point of D1S489 locus.

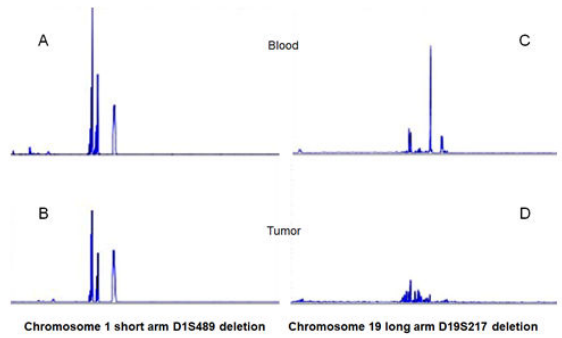

Figure 1: Fluorescence PCR capillary electrophoresis for detecting 1p/19q co-deletion. Comparison of the signals from blood samples (A, C) and from glioma tissues (B, D) for detecting the short arm of chromosome 1 (1p) (A, B) and the long arm of chromosome 19 (19q) (C, D).

The peak point of D1S489 in tumor tissue reduced more than 50% when comparing with that in the peripheral blood sample. Meanwhile, the existence of 1p/19q co-deletion could be determined when a clear peak point of D19S217 locus was in the tumor tissue, but it disappeared in the peripheral blood sample (Figure 1, C and D).

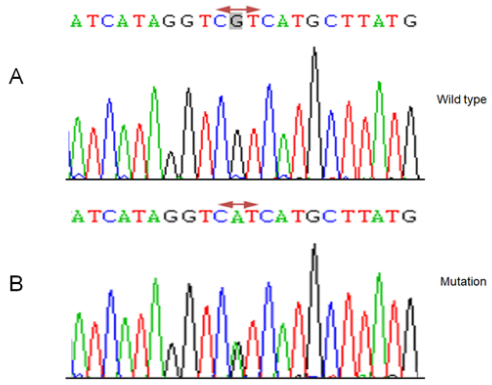

Figure 2: The p.R132H mutation in *IDH1* gene. DNA Sequencing of *IDH1* gene in a control/normal individual (A) and in a glioma patient (B). The mutation of G>A (CGT → CAT) transition at nucleotide position 395 results in Arg → His at codon 132 (p.R132H).

Determination of IDH mutation

The IDH locus in the tumour tissue was determined by sequencing. The *IDH1* gene is located at base 299, 394 and 195 in the long arm of chromosome 2, while *IDH2* gene is located at base 418, 419, 514, 515 and 516 in the long arm of chromosome 15.

The base G is at nucleotide position 395 of the wild type *IDH1* gene in one of our research cases (Figure 2A). When G changed to C, at this position (Figure 2B), the codon 132 of the *IDH1* gene changes from

CGT to CAT, resulting in replace of arginine by histidine (*IDH1* R132H: nucleotide 395 G>A) [11,12].

IDH mutation and 1p/19q co-deletion in different histological types of glioma

Within all 136 glioma patients, 39 cases (28.7%) were with the IDH mutation (37 cases in *IDH1*-mt and 2 with *IDH2*-mt) (Table 1A), and 47 cases (34.6%) with 1p/19q co-deletion (Table 1B). The statistically significant differences of the IDH mutations were between three pathological types of glioma, astrocytoma (AA), pure oligodendroglial tumors including both OA and AOA, and mixed glioma (OA+AA) (p=0.008). The statistically significant differences of the 1p/19q co-deletion was also found between groups of astrocytoma, pure oligodendroglial tumors, and mixed glioma (p=0.011). In three glioma types, the rate of 1p/19q co-deletion was highest in the group of pure oligodendroglial tumors (p=0.040) (Table 1B).

Type of glioma	IDH-wt	IDH-mt	Total
Astrocytoma	63 (81.8%)	14 (18.2%)	77 (100.0%)
Pure oligodendroglial tumors	6 (54.5%)	5 (45.5%)	11(100.0%)
Mixed glioma	28 (58.3%)	20 (41.7%)	48 (100.0%)
Total	97 (71.3%)	39 (28.7%)	136 (100.0%)

Table 1A: Genetic detection in different histological types of glioma: IDH mutations in different histological types of glioma.

Type of glioma	1p/19q non-codeletion	1p/19q codeletion	Total
Astrocytoma	56 (72.7%)	21 (27.3%)	77 (100.0%)
Pure oligodendroglial tumors	3 (27.3%)	8 (72.7%)	11(100.0%)
Mixed glioma	30 (62.5%)	18 (37.5%)	48 (100.0%)
AA: Astrocytoma; Pure oligodendroglial tumors=OA (oligodendroglioma) plus AOA (anaplastic oligodendroglioma); Mixed glioma=OA and AA; wt: Wild type; mt: Mutation.			

Table 1B: Genetic detection in different histological types of glioma: 1p/19q codeletion in different histological types of glioma.

Difference between genetic detection and morphological diagnosis

In a total of 136 glioma patients, 97 cases (71.3%) were detected as IDH-wt with 74 (54.4%) of 1p/19q non-codeletion and 23 (21.3%) of 1p/19q codeletion, and 39 (28.7%) as IDH-mt with 19 (13.9%) of 1p/19q non-codeletion and 20 (14.7%) of 1p/19q codeletion (Table 2). In the group of pure oligodendroglial tumors (n=11), 6 cases (54.5%) were as IDH-wt with 3 (27.3%) of 1p/19q non-codeletion and 03 (27.3%) of 1p/19q codeletion, and 5 (45.5%) as IDH-mt with 1p/19q codeletion (Table 2). The results indicate that, in 11 patients who were histopathologically diagnosed as oligodendroglioma, only 5 cases meet the WHO criterion that requires the presence of both 1p/19q codeletion and *IDH1*-mt or *IDH2*-mt [5].

IDH	1p/19q	Astrocytoma	Pure oligodendroglial tumors	Mixed glioma	Total
IDH-wt	1p/19q non-codeletion	49 (63.6%)	3 (27.3%)	22 (45.8%)	74 (54.4%)
	1p/19q codeletion	14 (18.2%)	3 (27.3%)	6 (12.5%)	23 (21.3%)
IDH-mt	1p/19q non-codeletion	7 (9.1%)	0 (0.0%)	8 (16.7%)	19 (13.9%)
	1p/19q codeletion	7 (9.1%)	5 (45.4%)	12 (25.0%)	20 (14.7%)
	Total	77 (100.0%)	11 (100.0%)	48 (100.0%)	136 (100.0%)
AA: Astrocytoma; Pure oligodendroglial tumors=OA (oligodendroglioma) plus AOA (anaplastic oligodendroglioma); Mixed glioma=OA and AA; wt: Wild type; mt: Mutation.					

Table 2: Association between IDH mutations and 1p/19q dodeletion.

Discussion

Our initial aim was to assess the diagnostic difference between the histopathological methods and genetic detections for IDH mutations and 1p/19q codeletion in glioma, especially oligodendroglial tumors. This study presents that, in a total of 136 patients with astrocytoma, pure oligodendroglial tumors (oligodendrogliomas) and mixed glioma, 28.7% of cases were detected with IDH mutations, including IDH 1-mt p.R132H and IDH 2-mt, and 34.6% of cases with 1p/19q codeletion. The highest rate of 1p/19q co-deletion was in oligodendroglioma cases with significant difference. In addition, we have found that only 45.5% of oligodendroglioma cases agreed with the WHO criteria of oligodendroglioma, both 1p/19q codeletion and IDH mutations.

With the research progress, more and more genomics parameters have been introduced into the diagnoses of glioma types [6,13]. In

2016, WHO once again revised the classification of the tumors of central nervous system. The definitions of astrocytoma and oligodendroglioma were redefined. The combination of IDH mutant and 1p/19q codeletion is a characteristic genetic change [3,7]. The achievements in the world, including China, indicate that glioma with 1p/19q codeletion are more sensitive to radiotherapy and chemotherapy, and usually with better prognosis [14-16]. Therefore, it is important to accurately identify oligodendrocytoma and astrocytoma, especially distinguish oligodendroglioma from mixed gliomas.

The incidence of IDH mutant and 1p/19q codeletion has been reported with significant differences in different subtypes of gliomas diagnosed by morphological methods. Especially, the rate of 1p/19q codeletion in oligodendrocytoma is significantly higher than that in astrocytoma [16-19]. Even in mixed glioma with features of oligodendrocyte and astrocytic, the rate of 1p/19q codeletion is still higher than that in astrocytoma [14,20]. Our results also agree with the previous reports. Furthermore, we find some patients with IDH-wildtype and 1p/19q codeletion in all three histological types of gliomas. The observation might be related to the origin and differentiation of glioma. We also note that, in the group of oligodendroblastoma, 54.6% (6/11) cases have been found with IDH mutation but 1p/19q non-codeletion, which means that some results of the genetic test did not support the histopathological diagnosis. Therefore, the genetic test should be complemented with the histopogical typing of gliomas, especially for oligoastrocytomas.

Conclusion

In conclusion, we have found that the rate of IDH mutations (IDH 1-mt and IDH 2-mt) and 1p/19q codeletion is significantly different in three groups of astrocytoma, pure oligodendroglial tumors (oligodendrogliomas) and mixed glioma diagnosed by histopathological methods, and highest in the group of oligodendrogliomas. We have also found some cases of oligodendrogliomas with only IDH mutation but without 1p/19q codeletion. Therefore, the genetic detections should be complemented for diagnosis of gliomas.

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