Research Article

IDH Mutations: Genotype-Phenotype Correlation and Prognostic Impact

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Received 14 February 2014; Accepted 7 April 2014; Published 30 April 2014

Academic Editor: Emeline Tabouret

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IDH1/2 mutation is the most frequent genomic alteration found in gliomas, affecting 40% of these tumors and is one of the earliest alterations occurring in gliomagenesis. We investigated a series of 1305 gliomas and showed that IDH mutation is almost constant in 1p19q codeleted tumors. We found that the distribution of IDH1R132H, IDH1nonR132H, and IDH2 mutations differed between astrocytic, mixed, and oligodendroglial tumors, with an overrepresentation of IDH2 mutations in oligodendroglial phenotype and an overrepresentation of IDH1nonR132H in astrocytic tumors. We stratified grade II and grade III gliomas according to the codeletion of 1p19q and IDH mutation to define three distinct prognostic subgroups: 1p19q and IDH mutated, IDH mutated—which contains mostly TP53 mutated tumors, and none of these alterations. We confirmed that IDH mutation with a hazard ratio = 0.358 is an independent prognostic factor of good outcome. These data refine current knowledge on IDH mutation prognostic impact and genotype-phenotype associations.

1. Introduction

The WHO Classification of Tumors of the Central Nervous System is the universal standard for classifying and grading brain neoplasms [1]. According to the presumed cell of origin, gliomas have been classified into three major groups: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Based on the presence or absence of malignant features: cell density, nuclear atypia, mitosis, microvascular proliferation, and necrosis, the WHO classification distinguishes grades I, II (LGG), III (anaplastic), and IV (glioblastomas, GBM) [2]. However, this classification suffers from a lack of reproducibility, with a high interobserver variability, often leading to discordant results between centers [3–5].

In these settings, there is a need for the identification of additional prognostic markers to refine the WHO classification in order to define more homogeneous subgroups. Mutations in the IDH1 (isocitrateg dehydrogenase 1) gene have been first reported in 2008 [6]. Since then, the IDH1 mutation has been recognized as the most frequent alterations in gliomas, occurring in 40% of glial tumors [7–9] and is the most powerful prognostic factor ever described in gliomas [10, 11]. Less frequently the mitochondrial isoform IDH2 is mutated.

We have investigated the mutational status of IDH1 and IDH2 in a cohort of 1305 glioma patients and correlated it with the genomic profile and the outcome.
2. Patients and Methods

2.1. Patients and Tissue Samples. Patients were selected retrospectively according to the following criteria: histologic diagnosis of grade II to grade IV glioma; clinical data and follow-up available in the neurooncology database; and written informed consent. The inclusion period extends from May 1987 to October 2010. Tumor DNA was extracted from both frozen and paraffin embedded formalin fixed tumors, when available, using the QIAamp DNA minikit, as described by the manufacturer (Qiagen). CGH-array analysis, LOH (loss of heterozygosity) analysis, EGFR amplification, and PI6 deletion assessment were performed as previously described [12].

2.2. Determination of IDH1 and IDH2 Mutational Status. The genomic regions spanning wild-type R132 of IDH1 and wild-type R172 of IDH2 were analyzed by direct sequencing using the following primers: IDH1f 5-AGAAGAGGGTTGAGGAGTCTGGGATCGAGTTCAA, IDH1r 5-CACATACAAGTTGGAAATTTCTGG, IDH2f 5-AGCCCATCATCTGCAAAAAC, and IDH2r 5-CTAGGCCGAGGCTCCAGT, as previously described[14]. Forward and reverse chains were analyzed on an ABI prism 3730 DNA analyzer (Perkin Elmer).

IDH2 mutational status was determined by Sanger sequencing and by PCR HRM. The latter approach allowing only the detection of an IDH2 mutation presence, we have only the type of base substitution for 15 tumors. HRM was performed as previously described [13].

2.3. MGMT Status and TP53 Mutations Determination. DNA methylation status of the MGMT promoter was determined by bisulfite modification and subsequent nested MSP, a two-stage PCR approach, as previously described [14]. TP53 gene mutations were screened for exons 5–8 by using previously reported primers and methods [15].

2.4. Statistical Analysis. The χ² test (or Fisher’s exact test when one subgroup was <5) was used to compare the genotype distribution. The association with continuous variables was calculated with a Mann-Whitney test.

Overall survival (OS) was defined as the time between the diagnosis and death or last follow-up. Patients who were still alive at last follow-up were considered as a censored event in analysis. Progression free survival (PFS) was defined as the time between the diagnosis and recurrence or last follow-up. Patients who were recurrence-free at last follow-up were considered as a censored event in analysis. To find clinical and/or genomic factors related to OS (or PFS), survival curves were calculated according to the Kaplan-Meier method and differences between curves were assessed using the log-rank test. Variables with a significant P value were used to build multivariate Cox model.

3. Results

We have screened for the presence of codon-132 mutations in the IDH1 gene in a large cohort of 1305 gliomas, including 436 WHO grade II, 394 WHO grade III, and 475 WHO grade IV gliomas. The presence of IDH2 mutation was investigated in a cohort of 980 gliomas (379 grade II, 289 grade III, 312 grade IV). In the whole cohort, sex ratio was 1.3 and median age at diagnosis was 49.2 years (range, 16.1 to 89.1 years). The characteristics of the population are indicated in Table 1.

Taken together we found 609/1305 IDH1 and 30/980 IDH2 mutations (global mutation rates of 46.7% and 3.1%, resp.). No tumor harbored both IDH1 and IDH2 mutations (Supplementary Table 1 available online at http://dx.doi.org/10.1155/2014/540236). Patients with IDH1 mutations were younger for the whole series (median age 40.6 years for IDH1 mutated patients versus 55.9 years; P < 0.0001) and also for grades III and IV separately (median age at diagnosis 44.4 and 47.8 years for grades III and IV IDH1 mutated tumors, versus 51.5 and 59.0 years for grades III and IV nonmutated gliomas; P = 0.0012 and P < 0.0001, resp.).

3.1. Genotype-Phenotype Correlations. IDH1 mutations affected 72.5% (316/436) grade II, 63.7% (251/394) grade III, and 8.8% (42/475) grade IV gliomas. We looked then for association between glioma subtypes (astrocytic, mixed, and oligodendrogliomas) and IDH1R132H, IDH1K140R and IDH1K140Q mutations, and IDH2 mutations. In grades II and III gliomas, IDH2 mutations were overrepresented in oligodendrogliomas (22 IDH2 mutations out of 330 IDH2 mutated tumors; 6.7%), compared to astrocytomas (1/60; 1.7%) and mixed gliomas (6/176; 3.4%) (P = 0.049). In contrast, we found that IDH1R132H mutations were more frequent in astrocytic (6/60; 10.0% IDH1 mutated tumors) and mixed tumors (15/176, 8.5%), compared to oligodendrogial tumors (15/332, 4.5%, P = 0.037).
Table 2: Comparison of histologic distribution, molecular alterations, and prognostic impact between IDH mutated and wild type patients.

| Histologic subtypes | n | IDH1 mutated tumors* | IDH2 mutated tumors | IDH wild type tumors |
|---------------------|---|----------------------|---------------------|---------------------|
| Astrocytic tumors   |   |                      |                     |                     |
| AII                 | 448 | 87                   | 2                   | 359                 |
| AIII                | 61  | 43 (2)               | 1                   | 17                  |
| GBM                 | 33  | 17 (4)               | 0                   | 16                  |
| Oligodendrogial tumors | 584 | 347                  | 22                  | 215                 |
| OII                 | 243 | 182 (10)             | 15                  | 46                  |
| OIII                | 220 | 150 (5)              | 7                   | 63                  |
| GBMO                | 121 | 15 (1)               | 0                   | 106                 |
| Mixed tumors        | 275 | 176                  | 6                   | 93                  |
| OAII                | 134 | 92 (6)               | 5                   | 37                  |
| OAIII               | 141 | 84 (9)               | 1                   | 56                  |

| Molecular alterations | n | MGMT promoter methylation | EGFR amplification | Complete 10q loss | PI6 deletion | TP53 mutation |
|-----------------------|---|--------------------------|-------------------|-----------------|-------------|--------------|
| Overall survival      |   | 587                      | 195/256 (76.2%)   | 196/639 (30.7%) | 359/576 (62.3%) |
| Grade II             | 309 | 136.5                   |                   | 67.0a           |              |
| Grade III            | 303 | 136.9                   |                   | 20.1b          |              |
| Grade IV             | 435 | 26.6                    |                   | 14.2c          |              |
| Progression free survival | | | | | |
| Grade II             | 309 | 41.3                    |                   | 28.5d          |              |
| Grade III            | 303 | 31.9                    |                   | 10.4e          |              |
| Grade IV             | 435 | 10.0                    |                   | 8.1f           |              |

* For histologic subtypes, the number in parentheses indicates the number of IDH1mutR132H mutations. a,b,c,P < 0.0001; d,P = 0.0004; e,P = 0.0363; f,P = 0.0008.

3.2. IDH Mutations Are Associated with Tumor Genomic Profile. We have then evaluated the association of IDH mutation with the molecular alterations commonly found in gliomas (Table 2). We found that IDH mutations were significantly associated with MGMT promoter methylation (P < 0.0001). In contrast, there was a strong association between the absence of IDH mutation and complete loss of chromosome 10q, EGFR amplification and P16 deletion (P < 0.0001 in each case).

Complete lp19q codeletion was found in 150 gliomas: the IDH1 gene was mutated in 137 cases (91.3%) and the IDH2 gene was mutated in 12 of the 13 remaining tumors. Taken together, the IDH genes were altered in 99.3% (149/150) of the lp19q codeleted tumors.

TP53 mutation was analyzed by Sanger sequencing in 396 tumors: 64/178 (35.9%) IDH mutated tumors were also mutated on TP53, versus 46/175 (26.2%, P < 0.0001) in nonmutated gliomas.

3.3. IDH1 Mutation Is an Independent Prognostic Factor of Good Outcome. We investigated the prognostic impact of IDH status in grade II, grade III, and grade IV gliomas. For each grade, IDH mutated patients have significantly longer overall survival and progression free survival than IDH normal patients (Figure 1 and Table 2).

We then entered the following factors as candidate variables in the multivariate Cox proportional hazards regression model analysis: IDH mutation, P16 deletion, lp19q codeletion, extent of surgery, Karnofsky index, and age at diagnosis (Table 3). IDH mutation was a strong and independent predictor of a better outcome (hazard ratio for overall survival = 0.358; 95% CI, 0.248 to 0.517; P < 0.0001).

Moreover, as previously described [16], we stratified the grade II and grade III tumors according to lp19q codeletion and IDH status, thus defining three prognostic groups: lp19q codeleted (and IDH mutated), IDH mutated, and others (Figure 2).

Whatever the grade, patients harboring the lp19q codeletion have a significantly longer survival (median OS: 150.9 months) than patients only harboring IDH mutation (69.0 months) or none of these alterations (25.4 months). We looked then at TP53 mutation in these three prognostic groups...
Table 3: Multivariate Cox proportional hazards regression model analysis of survival of the 1305 glioma patients cohort. MGMT promoter methylation was not included in this analysis due to a low number of evaluable patients for this parameter.

| Parameter         | Overall survival | Progression free survival |
|-------------------|------------------|---------------------------|
|                   | HR               | 95% CI for HR | P   | HR            | 95% CI for HR | P   |
| Age > 60 years    | 1.831            | 1.358 to 2.467 | 0.0001 | 1.479        | 1.158 to 1.889 | 0.0018 |
| Surgery extent    | 0.775            | 0.588 to 1.021 | 0.0715 | 1.045        | 0.823 to 1.326 | 0.7199 |
| 1p19q codeletion  | 0.202            | 0.098 to 0.415 | <0.0001 | 0.491        | 0.326 to 0.739 | 0.0007 |
| IDH mutation      | 0.358            | 0.248 to 0.517 | <0.0001 | 0.467        | 0.348 to 0.627 | <0.0001 |
| IK > 70           | 0.419            | 0.315 to 0.556 | <0.0001 | 0.489        | 0.375 to 0.636 | <0.0001 |
| P16 deletion      | 1.513            | 1.168 to 1.960 | 0.0018 | 1.471        | 1.165 to 1.858 | 0.0013 |

Figure 1: Prognostic impact of IDH status on overall survival (a) and progression free survival (b) in grade II to IV gliomas.
Figure 2: Overall survival (OS, (a)) and progression free survival (PFS, (b)) for grade II and III gliomas patients stratified according to 1p19q codeletion and presence of IDH mutations. Median OS were 150.9, 69.0, and 25.4 months for 1p19q/IDH mutated, IDH mutated, and other groups, respectively. Median PFS were 51.1, 34.3, and 12.2 months for 1p19q/IDH mutated, IDH mutated, and other groups, respectively.

Table 4: Association of TP53 mutation with 1p19q codeleted tumors and IDH mutated tumors.

|      | Mutated | Normal | Percentage | Difference to IDH mutated group (P) |
|------|---------|--------|------------|-------------------------------------|
| Grade II | 1p19q/IDH mutated | 3 | 31 | 8.8% | <0.0001 |
|       | IDH mutated       | 31 | 22 | 58.5% | — |
|       | others            | 5 | 13 | 27.8% | 0.0309 |
| Grade III | 1p19q/IDH mutated | 1 | 16 | 6.3% | 0.0002 |
|        | IDH mutated       | 21 | 13 | 61.8% | — |
|        | others            | 11 | 24 | 31.4% | 0.0160 |

The association of IDH mutation with TP53 mutation has been widely studied in literature and has led to contradictory results. IDH mutation was found associated with TP53 mutation in several studies [11, 18, 20–24] but other authors did not find such an association [10, 25]. We found an association between IDH and TP53 mutations, but we showed TP53 mutation correlated with astrocytic phenotype, in contrast with IDH mutation more associated with the oligodendroglial phenotype. Therefore, when excluding 1p19q codeleted tumors, mostly oligodendrogial, and rarely TP53 mutated, we found a stronger positive association between IDH and TP53 mutations. This result is concordant with the data of Gravendeel et al. who found a correlation between TP53 mutation and $IDH1^{nonR132H}$ mutation [26].

Confirming previous data obtained on smaller cohorts [10, 16], our findings showed that gliomas patients harboring an IDH1 mutated tumor present an improved outcome, compared to patients with an IDH1 normal tumor. The multivariate analysis shows that IDH status is an independent prognostic factor in a 1332 glioma patients cohort. To further explore the prognostic impact of IDH1 mutation, we subdivided both grade II and III gliomas patients in three prognostic subgroups, based on the 1p19q codeletion groups and found P53 mutation strongly associated with group 2 in both grades II and III (Table 4). For example in grade II gliomas, TP53 was mutated in 58.5% in group 2, versus 8.8% and 27.8% in groups 1 and 3, respectively ($P < 0.0001$ and $P = 0.031$, resp.).

4. Discussion

In this large series, we investigated the place of IDH1/IDH2 mutation in gliomas, in particular in different genotypes and phenotypes. As a first result, we confirmed the strong association of IDH mutations with the tumor genomic profile [10]: virtually all 1p19q codeleted tumors are IDH mutated [17, 18] whereas IDH mutation is extremely rare in gliomas with EGFR amplification. Secondly, we showed that the type of mutation is related to the molecular profile. The $IDH1^{R132H}$ mutation represents 90% of all IDH mutations. However, we found here that $IDH1^{nonR132H}$ mutations are associated with astrocytic tumors [19], whereas IDH2 mutations are associated with oligodendrogliomas. The 1p19q codeletion is a hallmark of oligodendroglial phenotype and we found similar results when tumors are stratified according to histological subtype.
and IDH mutation status ((i) IDH mut/1p19qdel, (ii) IDH mut/1p19qnon del, (iii) IDH non mut/1p19qnon del.). In line with a recent study [22], we found that TP53 mutation characterizes the group 2 (IDH mut non 1p19q codeleted). The third group with the worst prognosis contains mainly triple negative gliomas (non 1p19q codeleted, non IDH mutated, non TP53 mutated) [22].

Taken together, our results show that IDH mutation combined with other genomic marker can be used to refine the prognostic classification of gliomas, independently of tumor grade. With the recent results of randomized trial, IDH1 mutation has become, with 1p19q codeletion, a predictive marker of the response to chemotherapy [27–29].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This paper is supported by Grants from the Institut National du Cancer (INCA; PL 046) and the Ligue Nationale contre le Cancer. The authors are indebted to Anne-Marie Lekiefre and Muriel Brandel for their assistance in the study. All authors had full access to the original data, reviewed the data analyses, read, and approved the final paper.

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