Microsatellite Instability Occurs in Distinct Subtypes of Pediatric but not Adult Central Nervous System Tumors

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ABSTRACT

Length alterations in microsatellite repeats, termed microsatellite instability (MSI), are found in 10–15% of sporadic colon, endometrial, and gastric cancers harboring defects in DNA mismatch repair (MMR) genes. We used the microsatellite markers Big Adenine Tract (BAT) 26 and BAT-25 from the reference panel of five markers recommended by the National Cancer Institute to evaluate the incidence of MSI in 206 central nervous system tumors. We screened 102 pediatric and 104 adult cases representing 165 astrocytic and 41 nonastrocytic tumors. The overall incidence of MSI was 8% (16 of 206). All 16 tumors with MSI were found in pediatric rather than adult patients. MSI was associated with two distinct subtypes of pediatric tumors occurring in 27% (12 of 45) of WHO grade III and grade IV astrocytomas and 24% (4 of 17) of ganggliogliomas. We evaluated the difference in clinicopathological and genetic features among 45 high-grade pediatric astrocytomas by MSI status. The median survival for pediatric patients with MSI (n = 12) was 8 months compared with 15 months for those patients without MSI (n = 33; P = 0.18). The frequency of p53 gene mutations was 13% for pediatric patients with MSI (n = 8) compared with 47% for those patients without MSI (n = 19; P = 0.19). These results revealed a trend between MSI status and prognosis and MSI status and frequency of p53 gene mutations. Our data suggest that pediatric high-grade astrocytomas can be attributed to two different genetic pathways: a MMR-deficient pathway and a MMR-proficient pathway.

INTRODUCTION

Microsatellites are short, tandemly repeated nucleotide sequences that are widely distributed throughout the genome (1). Length alterations in mono-, di-, tri-, tetra-, and pentanucleotide repeats, termed MSI1, are used as a diagnostic criterion of the defective RER phenotype. Defective RER is most commonly caused by a deficiency of DNA MMR attributable to mutation in one of the human DNA MMR genes: hMLH1, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2 (2–8). Because of their repetitive nature, microsatellites are particularly prone to errors during replication. Thus, the RER phenotype, characterized by frequent somatic variations in the size of microsatellites in tumor DNA, results in MSI (9).

MSI was initially described in a minority (~15%) of nonsellected colon tumors (9, 10) and in a majority (>90%) of HNPCC tumors (11). MSI has also been described in other sporadic tumors such as gastric and endometrial cancers (8, 12). Nonsellected tumors necessarily contain both sporadic and hereditary cases, if a sufficient number is analyzed. Several studies have assessed gliomas for MSI using different panels of microsatellite loci, with conflicting results concerning the prevalence of the RER phenotype: reported incidences ranged from 1.8 to 45% (13–17). The difference in frequency of MSI noted in gliomas among these studies may be related to the sensitivity of the methods used to detect the status of MSI.

To assess the incidence of MSI in tumors of the CNS for which we did not have matching normal DNA, we used the mononucleotide microsatellite markers BAT-26 and BAT-25 from the reference panel of five markers recommended by the NCI Workshop on International Criteria for the Determination of Microsatellite Instability (12). Recent studies have shown that deletions within the mononucleotide microsatellite marker BAT-26, a poly(A) tract localized within intron 5 of the hMSH2 gene, is sufficient to establish the MSI status of most tumors in the absence of matching germline DNA (18–20). Deletions in BAT-26 were examined in 542 tumors from various organs, including colorectal, gastric, and endometrial cancers that had previously been assessed for MSI using di- and tetranucleotide microsatellite repeat markers; the MSI status was identified by BAT-26 deletion unambiguously in 99% (539 of 542) of the tumors (19). A recent study using BAT-26 as one of five microsatellite markers to evaluate MSI in 22 gliomas from a selected subgroup of young adult Chinese patients found that 18% (4 of 22) showed high rates of instability at >40% of microsatellites tested, and all of these tumors showed deletions in BAT-26 (21). These results suggest that deletions in the BAT-26 marker can be used to define MSI in tumors of the CNS, as has been documented in other cancers (18, 19).

By using the microsatellite markers BAT-26 and BAT-25, tumors can be categorized as having MSI if both of the markers show variation in length. The aims of this study were (a) to evaluate a large series of primary tumors of the CNS for the incidence of MSI; (b) to compare the MSI status in adult and pediatric CNS tumors; (c) to determine the clinicopathological and genetic features associated with MSI-positive tumors; and (d) to determine the relevance of MSI to patient prognosis.

MATERIALS AND METHODS

Tumor Samples. Tumor samples were obtained from 206 patients who had surgery at New York University School of Medicine between 1977 and 1995. Histopathological grading for astrocytomas used the revised WHO classification scheme except that necrosis was required for a diagnosis of glioblastoma (22). This study included 165 astrocytic [12 grade I (all pilocytic), 10 grade II, 48 grade III, and 95 grade IV] and 41 nonastrocytic tumors (17 ganggliogliomas, 5 neurocytomas, and 3 gangglioleneurocytomas, 10 PNets, 1 ependymomas, 1 meningioma, 1 anaplastic oligoastrocytoma, and 1 fibrosarcoma) from 102 pediatric (<21 years of age) and 104 adult patients. Histological evaluation of the tumor sections estimated that tumor samples consisted of >90% tumor cells. DNA was extracted from frozen or paraffin-embedded tissues as previously described (23, 24).

DNA Amplification by PCR. PCR was performed using a 1-μl sample of DNA in 10 μl of reaction mixture containing 10 μM Tris (pH 8.3), 1.5 μM MgCl2, 50 mM KCl, 200 μM dNTPs, 0.5 U of Platinum Taq polymerase (Life Technologies, Inc., Rockville, MD), 1.0 μmol of each primer, and 0.02 μmol
showed deletions in both BAT-26 and BAT-25 microsatellite markers compared with P18, other, demonstrating that BAT deletions may be unique for a given tumor. Representative, show mutant BAT-26 and BAT-25 PCR products that differ in length from each positive for MSI if the tumors exhibited additional, faster migrating BAT-26 and BAT-25 showing altered mobility in primary CNS tumor samples. Tumor samples were scored without MSI to monitor the sensitivity of detection of BAT-26 and BAT-25 bands

carcinoma cell line LS174T and 80% DNA from the glioblastoma cell line U87 MG without MSI to monitor the sensitivity of detection of BAT-26 and BAT-25 bands indicating deletion in that microsatellite marker. Arrowheads, position of wild-type and mutant BAT-26 and BAT-25 PCR products demonstrating a characteristic ladder of bands that differ in size by 1 bp. Note that the four primary MSI colon tumor samples, H1-H4, show mutant BAT-26 and BAT-25 PCR products that differ in length from each other, demonstrating that BAT deletions may be unique for a given tumor. Representative pediatric CNS tumors scored with MSI (P18, SC2, SC4, SC10, SC11, GG1, and GG4) showed deletions in both BAT-26 and BAT-25 microsatellite markers compared with those tumors scored without MSI (P17 and P134).

of the forward primer labeled with [γ-32P]dATP (NEN Life Science Products, Boston, MA) using T4 polynucleotide kinase (Life Technologies, Inc.). The PCR conditions for amplification of BAT-26 and BAT-25 primers used an initial denaturation at 95°C for 10 min followed by 40 cycles consisting of denaturation at 95°C for 1 min, annealing at 60°C for 1 min, and extension at 72°C for 1 min. A final extension cycle at 72°C for 10 min was performed for completion of all the PCR reactions.

The primer sequences for amplification were as follows: BAT-26: sense, 5’-TGACTAATTTGTACCTGCC-3’; antisense, 5’-AACATTCAACATTTAACC-3’, which amplify a 121-bp DNA fragment containing a poly(A)$_{15}$ tract of intron 5 of the hMSH2 gene (25) and BAT-25: sense, 5’-TGCCCTCAGGAGATGAAGT-3’; antisense, 5’-TCTGATTATTACATTGCT-3’, which amplify a 125-bp DNA fragment containing a poly(A) tract of an intron in the c-kit oncogene (25).

Analysis of Microsatellite Markers. The PCR products were denatured by heating for 5 min at 95°C in formamide loading buffer (94% formamide, 0.05% bromphenol blue, 0.05% xylene cyanol, 20 mm EDTA, 0.08 M NaOH), cooled on ice for 20 min and loaded onto a 6% (for BAT-26) or 8% (for BAT-25) denaturing polyacrylamide gel (Life Technologies, Inc.). Gels were run on a sequencing electrophoresis apparatus (Life Technologies, Inc.) at room temperature for ~2 h 30 min at 65 W without cooling. Gels were dried for 30 min at 80°C on a gel dryer (Bio-Rad, Hercules, CA). Radiolabeled DNA fragments were visualized using a Bio-Rad Personal Molecular FX apparatus with Quantity One (Version 4.0.3) software.

Detection of Microsatellite Instability. The presence or absence of MSI was based on the detection of length alterations in both of the mononucleotide microsatellite markers BAT-26 and BAT-25. The colon cancer cell line, LS174T, and four primary colon tumors previously scored as MSI served as positive controls for deletions in both markers (26). The glioma cell line, U87 MG, in which both microsatellite markers remained unaltered in length, served as a negative control. Tumor samples were scored positive for MSI if the tumors exhibited additional, faster migrating BAT-26 and BAT-25 bands that demonstrated deletions in both of these microsatellite markers. Experiments to ascertain MSI were done independently two to three times for each genetic locus.

Immunohistochemistry. Tumor tissue from 15 high-grade spinal cord astrocytomas were immunostained and evaluated for levels of expression of p53, MDM2, p16${^{INK4a}}$, and EGFR proteins as described (27). The immunohistochemistry and p53 gene mutation data for the 27 high-grade pediatric astrocytomas have been reported previously (28).

Statistical Analysis. Proportions were compared between groups using Fisher’s exact test, and continuous variables were compared using the two-sample $t$ test. For the survival analysis, duration of follow-up was defined as the interval from initial diagnosis through patient death or the last official contact (scheduled follow-up or personal contact) as of July 1999. Survival distributions were estimated according to the method of Kaplan and Meier and compared by means of the log-rank test.

RESULTS

Frequency of MSI in Tumors of the CNS. We screened 102 pediatric and 104 adult tumors representing 165 astrocytic and 41 nonastrocytic tumors of the CNS for deletions in the mononucleotide microsatellite markers BAT-26 and BAT-25. Figure 1 shows representative tumor DNAs with and without length alterations for both the BAT-26 and BAT-25 microsatellite markers. The overall frequency for MSI was 8% (16 of 206; Table 1). A similar incidence for MSI occurred in 7% (12 of 165) of astrocytic as well as 10% (4 of 41) of nonastrocytic tumors ($P = 0.53$). A significant association was found between younger age and the presence of MSI. Among high-grade astrocytic tumors, no adult patients showed MSI compared with an incidence of 27% (12 of 45) in pediatric patients ($P < 0.001$).

Among nonastrocytic tumors, there were 37 pediatric and 4 adult cases screened for MSI. Twenty-four percent (4 of 17) of the gangliogliomas were positive for BAT-26 and BAT-25 deletions. The 4 tumors occurred in pediatric patients ranging in age from 1 to 11 years. No deletions of BAT-26 and BAT-25 were detected in 24 other nonastrocytic tumors including 10 PNETs, 5 neurocytomas, 3 ganglioglioneurocytomas, 3 ependymomas, a meningioma, an anaplastic oligoastrocytoma, and a fibrosarcoma (Table 1). Presence of MSI was associated with younger age in the nonastrocytic tumors because no adult showed deletions of BAT-26 and BAT-25 (0 of 4) compared with 11% (4 of 37) of the pediatric patients. However, this difference was not statistically significant ($P = 1.00$) because of the small sample size.

Clinicopathological and Genetic Features of Pediatric High-grade Astrocytic Tumors by MSI Status. Table 2 gives the clinicopathological and genetic features of each of the 12 MSI high-grade astrocytic tumors. Figure 2 shows the Kaplan-Meier survival estimates. The median survival among patients with MSI ($n = 12$) was 8 versus 15 months for the patients without MSI ($n = 33; P = 0.18$).

Tumor tissue from 42 pediatric high-grade astrocytomas were evaluated for $p53$ gene mutations and levels of expression of EGFR, MDM2, and p16${^{INK4a}}$ proteins using immunohistochemistry as de-

<table>
<thead>
<tr>
<th>Frequency of MSI in tumors of the central nervous system</th>
<th>Tumor type</th>
<th>WHO grade</th>
<th>No. of cases</th>
<th>Deletion frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytic ($n = 165$)</td>
<td>Adult</td>
<td>IV</td>
<td>70</td>
<td>0/70 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>28</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>2</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>IV</td>
<td>25</td>
<td>7/25 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>20</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>8</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>12</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Nonastrocytic ($n = 41$)</td>
<td>Gangliogliomas</td>
<td>17</td>
<td>4/17 (24%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PNETs$^a$</td>
<td>10</td>
<td>0/10 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurocytomas</td>
<td>5</td>
<td>0/5 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganglioglioneurocytomas</td>
<td>3</td>
<td>0/3 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ependymomas</td>
<td>3</td>
<td>0/3 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other$^a$</td>
<td>3</td>
<td>0/3 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ PNETs, primitive neuroectodermal tumors.

$^a$ Other, meningioma, anaplastic oligoastrocytoma, and fibrosarcoma.

Table 1
scribed (27). The results for p53 gene mutations, EGFR and MDM2 protein overexpression, and loss of p16\(^{INK4a}\) expression have been reported previously for 27 cases (28). The frequency of p53 gene mutation was 13% (1 of 8) for pediatric patients with MSI compared with 47% (9 of 19) of those patients without MSI \((P = 0.19)\). For other clinical and genetic parameters such as gender, age, and levels of protein expression for EGFR, MDM2, and p16\(^{INK4a}\), no statistical significance was observed by MSI status (data not shown).

### DISCUSSION

Several studies have assessed gliomas, mainly adult fibrillary astrocytomas, for MSI using different panels of microsatellite loci with conflicting results. One aim of this study was to evaluate CNS tumors for the incidence of MSI using the microsatellite markers BAT-26 and BAT-25 from the reference panel of five markers recommended by the NCI for determining MSI (12). In this study, the presence or absence of MSI was based on the detection of bands with altered mobility, which indicate a deletion in both of the mononucleotide microsatellite markers BAT-26 and BAT-25. Recent studies suggest that in most instances in the absence of normal DNA, MSI can be determined by the analysis of a single microsatellite marker, BAT-26 (18–20). However, among healthy individuals of African origin, a polymorphic variation results in length alterations of BAT-26 and BAT-25 in \(~3\%\) of individuals at both loci (29). As far as we could determine, none of our patients were of African origin. We screened 102 pediatric and 104 adult tumors of the CNS for MSI. The overall incidence of MSI was 8% (16 of 206). There was a significant association between MSI status and patient age among both astrocytic and nonastrocytic tumors. Among patients with high-grade astrocytic tumors, no MSI was detected in adults compared with MSI in 27% (12 of 45) of pediatric patients \((P < 0.001)\). Among patients with non-astrocytic tumors, no adult showed deletions of BAT-26 and BAT-25 \((0 of 4)\) compared with deletions of BAT-26 and BAT-25 in 11% \((4 of 37)\) of pediatric patients \((P = 1.00)\).

MSI was present in two pediatric tumor subtypes: 27% \((12 of 45)\) of high-grade astrocytomas and 24% \((4 of 17)\) of gangliogliomas. Only three other studies have looked at these tumor subtypes. One reported screening 22 pediatric high-grade astrocytomas for MSI and finding an incidence of 9% \((2 of 22; \text{Ref. 30})\), another reported screening 6 pediatric high-grade astrocytomas for MSI and finding an incidence of 33% \((2 of 6; \text{Ref. 31})\), and a third reported screening 6 gangliogliomas for MSI, all from adults, and finding none positive for MSI (15).

Among the 16 MSI tumors, 12 were pediatric high-grade astrocytomas arising in patients ranging in age from 3 to 19 years \((\text{mean, 10.9 years})\). Turcot’s syndrome is a rare hereditary disease affecting children and young adults that is characterized by the presence of a brain tumor followed by the appearance of colorectal cancer (32, 33). Recent genetic studies have stratified Turcot’s syndrome patients into two distinct clinical subtypes based on the kind of colorectal cancer polyposis and the type of brain tumor detected (33). One clinical subtype consists of patients with a median age of 18 years who present with glioblastoma multiforme and colorectal adenomas with polyposis \((\text{non-FAP cases})\). Tumors from these patients show MSI similar to those from HNPCC patients with germline mutations in the DNA MMR genes \(hMSH2, hMLH1,\) and \(hPMS2\) (32–34). Since 1949 there have been only 160 cases of Turcot’s syndrome reported (22). Given the extreme rarity of glioblastomas associated with this syndrome, it is highly unlikely that the 12 cases of pediatric high-grade astrocytomas with MSI identified in this study are attributable to Turcot’s syndrome.

Another aim of this study was to evaluate the clinicopathological and genetic features of the 45 pediatric high-grade astrocytomas by MSI status. Some of the clinical features associated with MSI colon and gastric cancers are less frequent lymph node metastases, decreased wall invasiveness, and lower clinical aggressiveness of tumor growth with improved prognosis (35–37). We found that the median survival for pediatric patients with MSI \((n = 12)\) was 8 months compared with 15 months for those patients without MSI \((n = 33; P = 0.18)\). These results indicate a trend between MSI status and prognosis. A much larger study will be required to further examine the

### Table 2. Profile of genetic alterations in the MSI pediatric high-grade astrocytomas

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Tumor type</th>
<th>Age (y)/Sex</th>
<th>Survival (mo)</th>
<th>p53 IHC</th>
<th>p53 Mutation</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4</td>
<td>GBM</td>
<td>12/M</td>
<td>27</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P5</td>
<td>GBM</td>
<td>16/M</td>
<td>&lt;1</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P6</td>
<td>GBM</td>
<td>4/M</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P8</td>
<td>GBM</td>
<td>19/M</td>
<td>&lt;2, L</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P11</td>
<td>GBM</td>
<td>6/M</td>
<td>8</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P13</td>
<td>GBM</td>
<td>7/M</td>
<td>5</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P14</td>
<td>GBM</td>
<td>6/F</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>P18</td>
<td>AA</td>
<td>4/F</td>
<td>148, A</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SC2</td>
<td>AA</td>
<td>18/F</td>
<td>22</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>SC4</td>
<td>AA</td>
<td>17/F</td>
<td>10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>SC10</td>
<td>AA</td>
<td>3/F</td>
<td>9</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>SC11</td>
<td>AA</td>
<td>19/M</td>
<td>21</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* GBM, glioblastoma multiforme, WHO grade IV; AA, anaplastic astrocytoma, WHO grade III.

* IHC, immunohistochemistry; +, presence of protein; –, absence of protein; ND, not determined. Genetic alterations in tumors P4–P18 were previously reported (28).
relevancy of MSI status to prognosis of pediatric patients with high-grade astrocytomas. Studies of colorectal cancer have found that MSI status and p53 mutations are mutually exclusive genetic events (10, 38, 39). In this study, we found the frequency of p53 gene mutations was 13% for pediatric patients with MSI (n = 8) compared with 47% for those patients without MSI (n = 19; P = 0.19). This result reveals a trend between the presence of MSI and absence of p53 gene mutations, consistent with findings in other MSI tumors (38, 39).

Various sporadic cancers have been screened for MSI using criteria similar to the NCI panel of markers (12). Table 3 is a review of the published literature of sporadic tumors evaluated for MSI. For adult tumors of the CNS, MSI has been reported in 2% of astrocytic and nonastrocytic CNS tumors (13–15, 17, 19, 40–43). Thus, CNS tumors in adults show a low to zero incidence of MSI (15, 17, 19, 40, 42, 43). In contrast, for pediatric tumors of the CNS, MSI has been reported in 21% of astrocytic and 11% of nonastrocytic tumors (30, 31). MSI occurs in 10–15% of sporadic colon (19, 44–50), endometrial (51–53), and gastric (35, 54, 55) cancers compared with <5% of sporadic prostate (19, 56, 57), breast (44, 58), esophageal (59, 60), lung (55, 61, 62), and melanoma (63) tumors.

In summary, we have identified two distinct subtypes of pediatric CNS tumors that exhibit a high frequency of MSI compared with other sporadic cancers (Table 3). Overall, MSI occurred in 27% (12 of 45) of pediatric high-grade astrocytomas and 24% (4 of 17) of gangliogliomas. Future studies will investigate the genetic mechanism(s) associated with MSI in these tumors. Such mechanisms might include inactivating mutations of the MMR genes MLH1 or MSH2, promoter methylation of hMLH1, mutations leading to a dominant negative phenotype as has been demonstrated for the hPMS2 gene (4), or an imbalance in the levels of expression of one of the MMR genes such as hMLH3 (64), all of which result in MMR deficiencies. Glioblastoma formation in the adult has been attributed to two main genetic pathways: the p53-dependent “progressive” pathway (“secondary glioblastoma”) versus the p53-independent “de novo” pathway (“primary glioblastoma”; Refs. 24, 27, and 65). Using molecular genetic approaches, the constellation of altered target genes underlying the pathogenesis of different adult tumor variants are becoming known and thus can be exploited as potential therapeutic targets. In this study, we show that formation of high-grade astrocytomas in pediatric patients can be attributed also to two different genetic pathways: a MMR-deficient pathway versus a MMR-proficient pathway. A challenge for the future will be to identify the genetic differences between these pediatric glioblastoma tumor variants.

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