whereas patients with lesions in the left posterior inferior temporal area manifest alexia with agraphia for kanji only [10,23,24]. Functional MRI studies have shown that kanji processing activates wide areas in the dominant hemisphere [8,29].

Although many patients with glioma in the left hemisphere exhibit language deficits, the impairment of their language function has not been adequately studied. Therefore, we used the Japanese version of the WAB-J in the preoperative evaluation of these patients. Here, we report an important initial symptom among malignant glioma patients in good performance status.

2. Patients and methods

We subjected 17 patients with malignant glioma in the left hemisphere to the WAB-J at their admission for preoperative neurologic assessment (Table 1). All were native Japanese speakers, and none had a history of psychiatric or neurologic diseases. All patients were fully informed about the assessment and gave their prior written informed consent; the WAB-J was administered by one of the authors (TM) who complied with all guidelines. All patients underwent preoperative head MRI study to locate the brain lesions. Brain areas with tumor invasion were designated as additional lesions (Table 1). In all patients, the tumor was subtotally removed via craniotomy and submitted for histologic diagnosis. The patients were divided into 3 groups depending on the location of the lesions and their handedness because the language symptom is dependent on these 2 factors. Consequently, group 1 (cases 1-5) was right-handed and had left frontal glioma, group 2 (cases 6-14) was right-handed and had left temporal glioma, and group 3 (cases 15-17) was non–right-handed; their gliomas were in the left frontal or temporal lobe (Table 1).

3. Results

3.1. Clinical findings

The clinical data of our patients are summarized in Table 1. There were 8 men and 9 women; they were 55 ± 9.8 years of age (range, 38-76 years); 14 were right-handed, 2 (cases 15 and 16) were bimanual, and 1 (case 17) was left-handed. The chief complaints were difficulty in speech (n = 6), headache/nausea (n = 4), seizures (n = 5), uncinate fits (n = 1); one patient had no symptoms. Most of the patients had no motor deficits. The KPS of all patients exceeded 80 at admission. Illustrative MRI findings in patients with frontal and temporal glioma are shown in Fig. 2. Gd-enhanced MRI Gadolinium-enhanced T1-weighted MRI (Fig. 2A and C) showed typical ringlike enhancement. On T2-weighted MRI (Fig. 2B and D), peritumoral edema extended deep into the subcortical white matter. In 5 patients (cases 1, 4, 5, 7, and 15), there was tumor invasion into the insula; invasion by the frontal glioma into the temporal tip was seen in 4 patients (cases 1, 2, 4, and 16). Histologically, the tumor was identified as GB in 6 patients, as AA in 5, as AO in 1, as AOA in 4, and as grade 2 astrocytoma in 1 patient (Table 1).

3.2. Western Aphasia Battery profiles

Table 2 lists their scores for 7 sections of the WAB-J and their AQ. The AQ in all but 2 patients exceeded 80, indicating that overall, their language deficits were mild. Fig. 3 shows the average profile of each patient group for the 7 sections of the WAB-J. On the basis of the results of neurologic examination and the WAB-J guidelines [11], we judged that right-handed patients with frontal or temporal glioma-manifested anomic aphasia and that left-handed patients with frontal glioma exhibited a normal pattern.

In contrast to the overall profile, we found a marked reduction in the scores of 2 spelling-related tests in the reading

Table 2
Western Aphasia Battery scores of patients with glioma in the left hemisphere

Case no.	Content	Fluency	AC	Repetition	Naming	Reading	Writing	AQ
1	10	10	9.15	10	8.6	8.55	8.1	95.5
2	8	5	6.75	5.8	5.9	3.9	2.85	62.9
3	9	9	9.05	8.4	7.2	9	7.05	85.3
4	8	9	10	10	9	9.5	9.55	92.0
5	9	10	9.7	10	8.4	9.8	10	94.2
6	10	9	10	9.9	7.7	9.5	8.25	93.2
7	9	10	9.8	10	8.9	9.5	10	95.4
8	9	6	9.85	7.8	8.8	8.9	8.75	82.9
9	10	9	10	5.2	8	5.7	6.4	84.4
10	10	10	10	10	9.1	9.7	9.9	98.2
11	10	10	10	9.8	9.6	10	10	98.8
12	9	9	8.55	9.4	5.2	7.85	5.25	82.3
13	8	7	9.45	7.8	6.9	7.9	8.55	78.3
14	10	10	10	10	7.4	8.85	10	94.8
15	10	10	10	9.8	8.8	10	9.95	97.2
16	10	9	9.95	9.4	10	9.6	9.45	95.9
17	9	9	9.85	10	8.9	9.8	9.9	93.5

AC indicates auditory comprehension.

section (Fig. 4; see Fig. 1 for an explanation of these tests). In the "spelled kanji recognition" test (ie, recognizing orally spelled kanji; fifth item in Fig. 4), the average scores were reduced in all 3 groups (group 1—black bar, 5.3 ± 1.6; group 2—white bar, 6.1 ± 1.0; group 3—gray bar, 7.2 ± 2.0). In the "spelling kanji" test (sixth item in Fig. 4), the average scores were reduced in group 1 (3.0 ± 1.6, black bar) and group 2 (4.8 ± 1.2, white bar) but not in group 3 (9.4 ± 0.6, gray bar). The results of the kana-related tests (Fig. 5) showed normal profiles for all 3 groups, although group 1 exhibited a score reduction in the "picture stimulus" test (third item in Fig. 5). This finding was primarily because of the exceptionally low AQ of patient 2 (Table 2). It should be noted that spelling tests are only applicable for kanji characters because kanji are constructed with a few components, whereas kana have a single component (Fig. 1). Data from the reading section indicated that the scores of spelling tests were preferentially low in patients with glioma in the left hemisphere although their other aphasia symptoms may be mild.

4. Discussion

We preoperatively administered the WAB-J to Japanese patients with malignant glioma in the left hemisphere and found that a spelling deficit is an initial symptom of aphasia in these patients. Most of our patients did not manifest hemiparesis (Table 1), indicating that "kanji spelling" in Japanese patients reflects left hemisphere lesions more

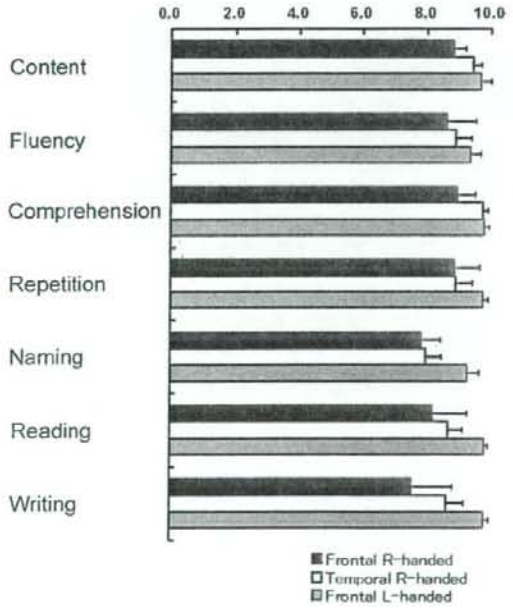

Fig. 3. Western Aphasia Battery subtest profiles of patients with glioma in the left hemisphere. Each test score was standardized so that the full score is 10. Scores are expressed as the mean (bars) ± standard error (error bars). Black, white, and gray bars are the scores of right-handers with frontal lesions, right-handers with temporal lesions, and left-handers or mixed-handers with frontal and/or temporal lesions, respectively.

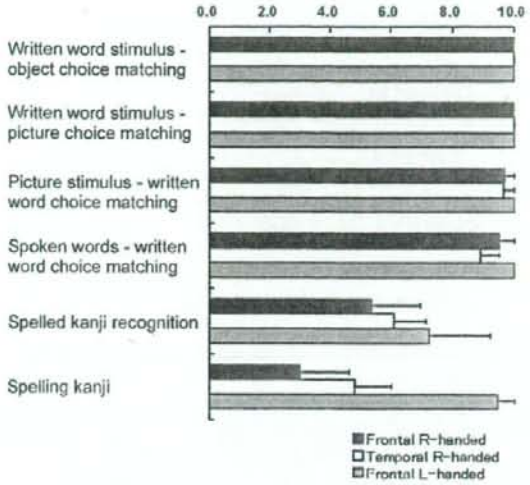

Fig. 4. Kanji test score profiles for the reading section of the WAB-J. "Written word stimulus—object choice matching" is the test for choosing the object that corresponds to the kanji description. "Written word stimulus—picture choice matching" is the test for choosing the picture that corresponds with the kanji description. "Picture stimulus—written word choice matching" is the test for choosing the kanji description that corresponds to the picture. "Spoken words—written word choice matching" is the test for choosing the kanji description that corresponds to the spoken word(s). "Spelled kanji recognition" is the test for recalling a kanji character from its parts. "Spelling kanji" is the test for separating a kanji character into its constituent parts. Scores are expressed as the mean (bars) ± standard error (error bars). The bars are as in Fig. 3.

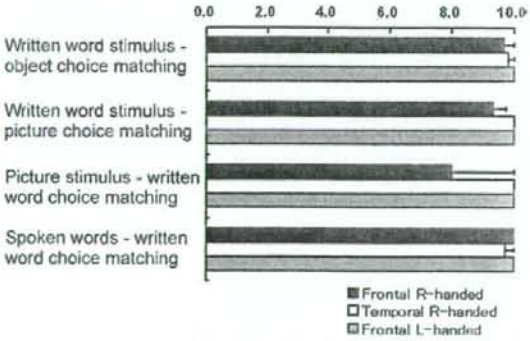

Fig. 5. Kana test score profiles for the reading section of the WAB-J. "Written word stimulus—object choice matching" is the test for choosing the object that corresponds to the kana description. "Written word stimulus—picture choice matching" is the test for choosing the picture that corresponds with the kana description. "Picture stimulus—written word choice matching" is the test for choosing the kana description that corresponds with the picture. "Spoken words—written word choice matching" is the test for choosing the kana description that corresponds with the spoken word(s). Scores are expressed as the mean (bars) ± standard error (error bars). Bars are as in Fig. 3.

sensitively than does motor function. Spelling tests can be performed easily during routine neuropsychological examination, and they are useful for the early diagnosis of patients seen at primary care facilities.

Most models of reading assume 3 major processing components defined as orthographic, phonological, and semantic lexicons. The orthographic lexicon is representation of previously encountered sets of letters and their order in each written word. The phonological lexicon is representation that specifies the pronunciation of previously encountered words or letter strings. The semantic lexicon is information about the meaning of these words. The traditional reading model (eg, Friedman et al [2]) argues that each of the 3 lexicons is assumed to function independently. The recently proposed model [19] postulated that the integrity of orthographic and phonological lexical representations depends upon a functioning semantic system. The semantic system is required for the flows of information between orthographic and phonological lexicons. The activation studies as well as lesion studies have been shown that the neural networks serving these 3 reading components are located widely in the frontal, temporal, and occipital cortices (reviewed by Noble et al [16]). According to the recent reading model, spelling tests in WAB-J (Fig. 1) should require the access not only to the phonological and orthographic lexicons but also to the semantic lexicon. Spelling was preferentially impaired in our patients regardless of whether the lesion was in the frontal or temporal lobes. Thus, our observation coincides with the reading model that suggests that the neural networks serving processing components for word spelling are located widely in the dominant hemisphere.

The patients with left frontotemporal-frontotemporal perisylvian lesions have deficits in spelling alphabetic words because of impaired phonological processing [4]. It would be important to investigate whether the spelling of alphabetic words is impaired early in the clinical course of patients with left frontotemporal invasive glioma. If true, then spelling deficits are a common initial symptom in patients with glioma in the left hemisphere, regardless of whether spelling involves phonograms (alphabet or kana) or ideograms (kanji). If false, then the observed spelling deficit may apply uniquely to ideograms. The results of such investigations will shed light on differences in the neural processes involved in the processing of ideograms and phonograms [9,10,22,24].

One of the most important questions to be discussed here is why the scores of reading tests related to Japanese ideogram (kanji) were selectively low. Electrical stimulation [33] and transcranial magnetic stimulation [31], which manipulate neuronal activity in the cerebral cortex, showed that the posterior inferior temporal area in the dominant hemisphere is of primary importance for kanji processing. Activation studies with fMRI or PET revealed that the left inferior temporal cortex plays an essential role in kanji orthographic and semantic processing [6,15,21,29]. Kato et al [8] investigated the activation patterns in the kanji-retrieval task; their study subjects were given part of a kanji and were required to complete the kanji. Functional MRI scans showed that the premotor cortex, presupplementary motor area, and the intraparietal sulcus were activated, indicating that the frontal lobe was involved in the kanji-retrieval task. They suggested that kanji retrieval elicits unintentional or automatic mental writing and that kanji processing is strongly associated with visuomotor neuronal representation. A study by Uchida et al [30] showed that the left inferior occipital gyrus, other than the primary or secondary visual cortex, plays an important role in the orthographic processing of kanji. These reports suggest that kanji processing requires neural networks residing in wide areas of the left hemisphere. It is also plausible that kanji processing is vulnerable to the lesion anywhere in the dominant hemisphere because of the wide distribution of processing component. The infiltrative nature of glioma cells may produce neurologic deficits by destroying neural networks not only in cortical regions but also in the subcortical white matter [35]. This hypothesis is supported by findings that resective surgery improves brain edema and consequently language function in dysphasic patients with tumors in the left hemisphere [28,35]. In our patients, the wide areas of left hemisphere were damaged by invasive glioma and exhibited high-grade peritumoral edema (Fig. 2). This may have resulted in the impairment of speech centers including cortical and subcortical structures involved in kanji processing.

5. Conclusion

Deficit in kanji spelling is one of the initial symptoms in Japanese patients with glioma in the left hemisphere. Spelling was preferentially impaired in our patients regardless of whether the tumor was in the frontal or temporal lobe. We posit that this reflected the vulnerability of the neural networks serving spelling function because of their wider distribution in the dominant hemisphere. In Japanese patients, the detection of spelling deficits is important for the early diagnosis of invasive malignant glioma in the left hemisphere. Furthermore, it would be important to determine whether the spelling of alphabetic words is similarly impaired early in the clinical course of patients with frontotemporal malignant glioma.

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Commentary

The authors present an interesting report of symptom presentation in patients with brain tumors, which are likely applicable in other neurologic conditions, as well, such as seizure, complicated migraine, and transient ischemic attack, and are of universal interest to all neuroscientists. As a neurologist, I am fascinated by the localization of the lesion in these cases, regardless of nature of the underlying disease, either structural or functional. As a neurooncologist, I am always sobered by the subtlety of presenting symptoms of a disease as serious disease as infiltrating glioma. I have 2 cases that come to mind—(1) a young woman who was an instructor in microbiology had absolutely no symptoms other than one day, while lecturing, she kept saying "P-8" instead of "pH." Fortunately, she did not dismiss this, as many might have, but sought medical attention to find a butterfly frontal lobe anaplastic oligodendroglioma and (2) a 40-year-old male, with a baseline highly somatic personality disorder, who presented for urgent MRI when he experienced a single event of upper lip numbness that lasted less than 1 minute and was found to have a lesion in the left temporal lobe, less than 2 mm, removed by gross total resection, and found to be GBM. Subtle symptoms, especially those that are brief and transient, or in a very specific cognitive domain, such as spelling or pronunciation, are important and should not be ignored by patients or dismissed by their physicians, though I suspect they are often overlooked until more dramatic and

obvious symptoms evolve. Unfortunately, in neurooncology, the only circumstance that "early detection" effectively impacts is that of a low-grade glioma that can be completely resected, thus reducing the chance of malignant transformation. I do not believe that there is such a thing as catching a glioblastoma multiforme early enough to result in a cure. My patient described above, with a 2 mm well-circumscribed, completely resected GBM, still died within 15 months of diagnosis. The insidious molecular transformations that silently occur in this disease do so well before enough parenchyma is affected to express itself in even the most subtle neurologic deficit, and early detection, early enough to achieve a true cure, remains elusive to us, at least for now.

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Single Nucleotide Polymorphism 309 Affects Murin-Double-Minute 2 Protein Expression But Not Glioma Tumorigenesis

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Abstract

Murin-double-minute 2 (MDM2) is an important negative regulator of the p53 tumor suppressor, and affects the p53 protein level and transcriptional activity. The genotype of the single nucleotide polymorphism in the promoter region of MDM2 (single nucleotide polymorphism [SNP] 309) is associated with the MDM2 protein expression level and the onset age of several types of cancer. The SNP309 genotype was investigated in 254 Japanese patients with glioma and 50 healthy subjects. The genotype frequency of SNP309 was T/T homozygous in 62 patients (24%), T/G heterozygous in 126 (50%), and G/G homozygous in 66 (26%) of the glioma patients, and was similar in the healthy subjects. The G/G ratio was higher in our Japanese subjects than in Western populations. Immunohistochemical study of glioma tissues showed that the G/G genotype was associated with higher expression of MDM2 protein compared to the T/T genotype, suggesting that SNP309 attenuates MDM2 protein expression in vivo. However, no association was found between the SNP309 genotype and the histological grade of glioma, age at disease onset, or p53 gene mutation rate. In our study population, SNP309 affected MDM2 protein level, but had no significant involvement in glioma tumorigenesis.

Key words: single nucleotide polymorphism, murin-double-minute 2, glioma

Introduction

The tumor suppressor gene p53 is known to affect many cellular functions such as cell-cycle arrest, apoptosis, and transcriptional regulation,[16] and is important in the suppression of glioma tumorigenesis. Approximately half of all examined gliomas manifested p53 mutation, and p53 inactivation is an early event of glioma tumorigenesis,[10] but the mechanisms underlying tumorigenesis in gliomas with wild-type p53 remain to be elucidated.

Murin-double-minute 2 (MDM2) is an important negative regulator of p53,[8] and MDM2 gene amplification was observed in 10–15% of malignant gliomas.[11] MDM2 overexpression leads to inhibition of p53-mediated transactivation and enhancement of tumor progression. In addition, MDM2 promotes rapid degradation of p53 protein via the ubiquitin-proteosome system.[8] As inactivation of p53 is an early event in glioma tumorigenesis, the expression level of MDM2 may be an important factor in tumor progression in gliomas with wild-type or mutant p53.

A single nucleotide polymorphism (SNP) in the promoter region of human MDM2 (SNP309) affects the binding activity of transcriptional factor Sp1 and attenuates the MDM2 messenger ribonucleic acid and protein expression level.[3] Moreover, the SNP309 genotype was associated with the onset age in several types of cancer. As p53 is important in glioma tumorigenesis and tumor progression, the SNP309 genotype may also be involved.

We examined the SNP309 genotype in Japanese patients with glioma and healthy subjects to determine whether there is a correlation between the expression of SNP309 and that of MDM2 and p53. We also analyzed the association between the SNP309 genotype and the age at onset and the

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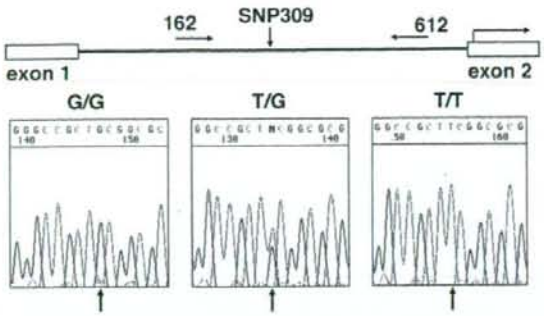

Fig. 1 Sequencing analysis of single nucleotide polymorphism (SNP) 309. *Upper*: SNP309 is located at the 309th nucleotide in the first intron of the murin-double-minute 2 gene, G is substituted for T. The arrows indicate the position of the primer sets and the amplified 451-bp fragment for direct sequencing of SNP309. *Lower*: Illustrative results of SNP309 direct sequencing. The arrows show the SNP309 peaks.

clinicopathological features of Japanese patients with glioma.

Materials and Methods

I. Deoxyribonucleic acid (DNA) samples

Genomic DNA from 254 Japanese patients with glioma, 150 males and 104 females aged 1–78 years (mean 47.7 years, median 51.0 years), and 50 healthy subjects, 25 males and 25 females aged 22–47 years (mean 32.2 years, median 31.5 years), was obtained from the Department of Neurosurgery of Kumamoto University Hospital and its affiliated hospitals. All protocols were approved by the Internal Review Board of Kumamoto University and prior informed consent was obtained from all patients and subjects. All histological diagnoses were confirmed by standard histological analysis of surgical specimens as previously described.[12] Of the 254 patients, 119 had glioblastoma, 51 anaplastic astrocytoma, 13 anaplastic oligodendroglioma, 30 anaplastic oligoastrocytoma, four anaplastic ependymoma, two anaplastic ganglioglioma, 14 pilocytic astrocytoma, 12 low grade astrocytoma, four oligodendroglioma, one oligoastrocytoma, and four ganglioglioma. Genomic DNA was extracted from whole blood using the QIAamp® DNA Mini Kit (Qiagen K.K., Tokyo), dissolved in 100 μl TE (10 mM Tris and 0.5 mM ethylenediaminetetra-acetic acid), and stored at 4°C until use. A pilot study showed complete matching between the genomic DNA extracted from blood samples and glioma specimens from 15 patients.

II. Identification of SNP309 genotype

To confirm sequence variations in the MDM2 promoter region, a 451 bp fragment that included SNP309 from genomic DNA was amplified and the 309th nucleotide in the first intron of the MDM2 gene was sequenced (Fig. 1). The forward and reverse primers were 5'-TTTTGTTGGACTGGGG-CTAG-3' and 5'-AGCAAGTCGGTGCTTACCTG-3', respectively. The polymerase chain reaction (PCR) products were separated by electrophoresis in 2% agarose gels and extracted with a PCR Purification Kit (Qiagen K.K.). Each fragment was sequenced on an ABI PRISM® 377 DNA Sequencer (PE Biosystems, Foster City, Calif., U.S.A.) using the ABI PRISM® Big Dye Terminator Cycle Sequencing Kit (PE Biosystems).

III. p53 Mutation analysis

The yeast functional assay was used as previously described.[12] Briefly, using p53 PCR products from the tissues of the patients as templates, the linearized p53-expression vector pSS16 was co-transfected into the yIG397 reporter yeast strain. The transformed yeast cells were plated, incubated at 30°C for 2 days to allow the formation of colonies, and stored overnight at 4°C for color development. At least 200 colonies were examined on each plate. If more than 15% of the colonies were red, we judged the sample positive for p53 functional loss and proceeded to sequence analysis.

IV. Expression of p53 and MDM2 protein

Formalin-fixed, paraffin-embedded tissue sections were cut, deparaffinized in xylene, rehydrated through a graded series of alcohol-to-water, and incubated for 5 minutes at room temperature with 0.3% hydrogen peroxide in distilled water to inhibit endogenous peroxidase. After washing with phosphate-buffered saline, the sections were completely immersed in 0.01 M citrate buffer (pH 6.0 and pH 7.0), processed for 15 minutes in a microwave oven at 500 W to enhance immunoreactivity, saturated with 10% normal serum for 20 minutes, and incubated at 4°C for 18–22 hours with monoclonal anti-human p53 protein (Ab-2, 1:50; Oncogene Research Products, Boston, Mass., U.S.A.) and monoclonal anti-human MDM2 protein (Ab-1, 1:50, SMP-14; Neomarkers Inc., Fremont, Calif., U.S.A.). Biotinylated antibody and Vectastain® Elite ABC (Vector Laboratories Inc., Burlingame, Calif., U.S.A.) were successively applied at room temperature for 30 minutes each. The immune reactions were developed with diaminobenzidine as the chro-

ogen. The sections were counterstained with matoxylin. Sections not exposed to the primary tibodies served as negative controls. The percenges of p53- and MDM2-positive tumor cells were timated by counting the number of immunoreacve cells in 10 high-power microscopic fields in eas with the highest visually determined immunositivity. The absence of any positive-signal tumor lls was scored as negative, <5% immunopositive mor cells as ±, 5–20% as +, 21–50% as ++, and 50% as +++.

Statistical analysis

All statistical analyses were conducted using MP® software (SAS Institute Inc., Cary, N.C., .S.A.). Statistical differences in variables were test- l by the χ^2 test. Genotype frequencies in all groups ere checked for Hardy-Weinberg equilibrium us- g the χ^2 test. Kaplan-Meier incident curves for the ree genotypes were used to analyze the age of glioa onset. The log-rank test was applied to compare e homogeneity of the incident curves between notype groups. A p value < 0.05 was considered significant.

Results

SNP309 genotype in the Japanese population

Investigation of genomic DNA from the 50 subcts found 15 (30%) were homozygous for T/T, 18 6%) were heterozygous for T/G, and 17 (34%) were omozygous for G/G. The frequencies were consisnt with Hardy-Weinberg equilibrium. Investigaon of genomic DNA from the 254 glioma patients und that 62 (24%) were T/T homozygous, 126 0%) were T/G heterozygous, and 66 (26%) were /G homozygous. These frequencies were also constent with Hardy-Weinberg equilibrium. There as no statistically significant difference between ioma patients and healthy subjects with respect to ie distribution of SNP309 genotype (p = 0.21, χ^2 st).

SNP309 genotype and expression of MDM2 and p53

A total of 54 glioma samples, 17 T/T, 22 T/G, and 5 G/G, were randomly selected and the expression f MDM2 and p53 examined (Fig. 2). Table 1 shows iat glioma homozygous for G/G expressed sigificantly more MDM2 protein than glioma homozyous for T/T (p = 0.0009, χ^2 test). In contrast, NP309 genotype had no effect on p53 protein xpression (p = 0.89, χ^2 test). Moreover, Table 2 ows no obvious correlation between the expreson of p53 and that of MDM2 (p = 0.57, χ^2 test).

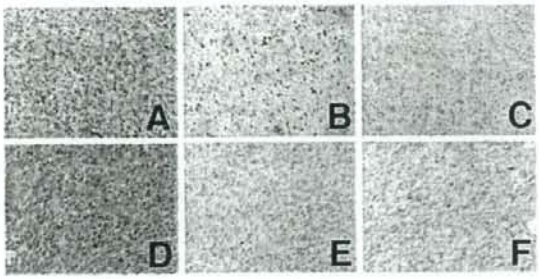

Fig. 2 Photomicrographs showing immunohistochemical examination of illustrative cases of glioblastoma with G/G genotype (A–C) and with T/T genotype (D–F). Hematoxylin and eosin stain (A, D), and immunohistochemical stain for murin-double-minute 2 (B, E) and p53 (C, F), ×200.

Table 1 Single nucleotide polymorphism (SNP) 309 genotype (T/T, T/G, G/G) and expression of murin-double-minute 2 (MDM2) and p53 in 54 glioma samples

	T/T (n = 17)	T/G (n = 22)	G/G (n = 15)
MDM2 expression			
− or ±	14	8	3
+ or ++	3	14	12
p53 expression			
− or ±	9	12	7
+ or ++	8	10	8

The SNP309 genotype affects the protein expression of MDM2 (p = 0.0009) but not that of p53 (p = 0.89, χ^2 test).

Table 2 Relationships between murin-double-minute 2 (MDM2) protein expression and p53 mutation, and p53 protein expression in 54 glioma samples

	p53 expression	
	− or ± (n = 28)	+ or ++ (n = 26)
MDM2 expression		
− or ±	14	11
+ or ++	14	15
p53 mutation		
−	25	5
+	3	21

Expression of p53 protein and p53 mutation were related (p < 0.001), but not MDM2 protein expression (p = 0.57, χ^2 test).

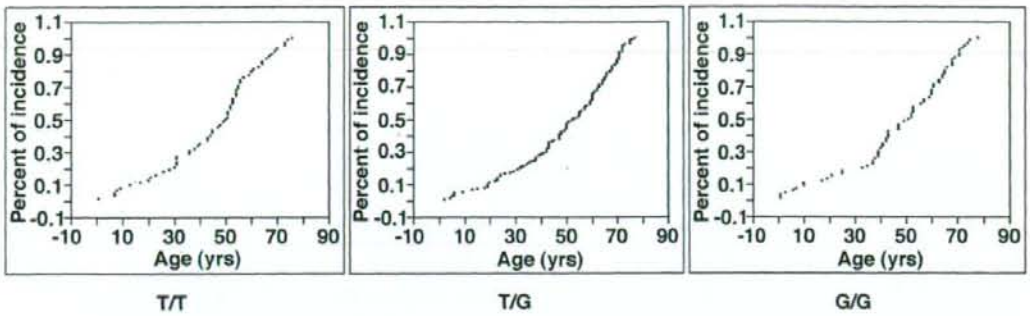

Fig. 3 Cumulative incidence and age at disease onset in 254 glioma patients.

Table 3 Classification of the 254 glioma patients according to the glioma grade and type, and the single nucleotide polymorphism (SNP) 309 genotype (T/T, T/G, G/G)

Histological classification	T/T (n = 62)	T/G (n = 126)	G/G (n = 66)
High grade (WHO grades III and IV)	54 (25%)	112 (51%)	53 (24%)
anaplastic astrocytoma	6	25	20
anaplastic oligodendroglioma	6	5	2
anaplastic oligoastrocytoma	7	20	3
anaplastic ganglioglioma	1	1	0
anaplastic ependymoma	0	3	1
glioblastoma	34	58	27
Low grade (WHO grades I and II)	8 (23%)	14 (40%)	13 (37%)
pilocytic astrocytoma	3	6	5
astrocytoma	3	4	5
oligodendroglioma	0	3	1
oligoastrocytoma	0	1	0
ganglioglioma	2	0	2

There was no significant association between SNP309 genotype and glioma grade and type ($p = 0.76$ for low grade glioma, $p = 0.14$ for high grade glioma, and $p = 0.21$ for all gliomas, χ^2 test). WHO: World Health Organization.

However, 21 of 26 gliomas with higher p53 expression had p53 gene mutations whereas 25 of 28 gliomas with lower p53 expression had wild-type p53, so there was a strong correlation between p53 gene status and protein expression ($p < 0.001$, χ^2 test). These findings suggest that the SNP309 genotype affects expression of MDM2 but not that of p53.

III. SNP309 genotype and clinicopathological features

We postulated that if SNP309 affects the pathway of p53 via MDM2 expression, the genotype may affect the clinicopathological features of the patients. Table 3 shows that there was no significant association between SNP309 genotype and glioma grade ($p = 0.76$ for low grade glioma and $p = 0.14$ for high grade glioma, χ^2 test). Table 4 shows that there was no association between the SNP309 genotype and mean ($p = 0.41$) or median age ($p = 0.71$) at glioma onset.

Table 4 Single nucleotide polymorphism (SNP) 309 genotype (T/T, T/G, G/G) and age at glioma onset in 254 glioma patients

Age	T/T (n = 62)	T/G (n = 126)	G/G (n = 66)
Mean (yrs)	45.2	49.2	47.3
Median (yrs)	50.5	52.5	51.5
Range (yrs)	1–76	2–77	1–78

There was no association between SNP309 genotype and mean ($p = 0.41$) or median age ($p = 0.71$, χ^2 test).

Figure 3 shows the cumulative incidence and age at onset, with no statistical difference between the SNP309 genotype and onset age ($p = 0.2776$, log-rank test). These results suggested that SNP309 genotype had no strong association with the age at

Table 5 Relationship between single nucleotide polymorphism (SNP) 309 genotype (T/T, T/G, G/G) and p53 mutation in 190 glioma patients

p53 mutation	T/T (n=47)	T/G (n=93)	G/G (n=50)
+	14	32	14
−	33	61	36

There was no association between SNP309 genotype and p53 mutation ($p = 0.70$, χ^2 test).

onset.

Although the inactivation of p53 is an early event in glioma tumorigenesis, our findings that the SNP309 genotype had no strong association with patient age at disease onset suggests that p53 mutation may mask the effect of SNP309 genotype on glioma progression. To test this hypothesis we examined the relationship between SNP309 genotype and p53 mutation in 190 of the 254 glioma patients (Table 5). However, we found no association between SNP309 genotype and p53 mutation ($p = 0.70$, χ^2 test). In addition, there was no association between the age at onset and SNP309 genotype in patients without p53 mutation (data not shown). Our results indicate that there was no strong association between the SNP309 genotype and patient age at onset, histological diagnosis, or p53 mutation.

Discussion

The presence of SNP309 homozygous for G/G affects the binding activity of the transcriptional factor Sp1 and results in higher MDM2 protein expression levels and attenuation of the p53 pathway.[3] Patients with Li-Fraumeni syndrome and sporadic soft tissue sarcoma who manifested SNP309 homozygous for G/G were younger at disease onset.[3] As p53 inactivation is an early event of glioma tumorigenesis, we analyzed the SNP309 genotype in our Japanese patients with glioma. Our immunohistological analysis showed that MDM2 protein expression was attenuated in the glioma tissues. However, we found no strong association between the SNP309 genotype and the histological diagnosis or the age at glioma onset. There is also no significant association between SNP309 genotype and age at disease onset in patients with other cancers.[1,4,6,7,14]

The SNP309 genotype distribution for Western populations is 48% T/T, 40% T/G, and 12% G/G.[3] Our study found a higher incidence of SNP309 homozygous for G/G in the Japanese population of 34% for healthy subjects and 26% for glioma patients. The reason is probably ethnicity-related differences in allele frequencies. The incidence of SNP309 homozygous for G/G was 24.8–29.3% in Chinese patients with breast and lung cancer,[6,7] similar to our patients and healthy subjects, and 13–24% in Caucasian patients with colorectal, breast, and ovarian cancer.[3,4,14] However, the incidence of SNP309 homozygous for G/G was also reported as 16–19% in the European Caucasian population.[4]

MDM2 is an important negative regulator for p53 protein and overexpression of MDM2, with or without gene amplification, is a genetic marker of primary glioblastoma without a p53 mutation,[11] but MDM2 overexpression and p53 mutation may not be mutually exclusive events. Our study found that gliomas with SNP309 homozygosity for G/G exhibited relatively higher levels of MDM2 protein, but there was no correlation between p53 protein expression and p53 mutation rate. Our immunohistochemical study showed that overexpression of p53 protein depended on the mutated gene status, not on MDM2 overexpression, suggesting that mutation of the p53 gene strongly affects p53 protein expression and overcomes the protein degradation caused by MDM2. MDM2 regulates p53 by two mechanisms: promotion of the rapid degradation of p53 protein by the ubiquitin-proteosome system, and direct binding to p53 and inactivation of the transactivating capability.[8] Transcriptional inactivation of p53 occurs via a p53-MDM2 binding complex and p53 is not excessively degraded even in cells with SNP309 homozygous for G/G.[2] Therefore, it is not surprising that tumors, especially gliomas, may overexpress both MDM2 and p53 and that overexpression of MDM2 and p53 mutation are not mutually exclusive.

The G allele of SNP309 is associated with lower age of onset in patients with sporadic soft tissue sarcoma,[3] but the present study found no strong association between the SNP309 genotype and the patient age at glioma onset. Patients with soft tissue sarcoma tend to be younger than patients with glioma at disease onset. In fact, most soft tissue sarcomas develop during childhood whereas gliomas tend to occur in individuals older than 50 years. There is a strong correlation between p53 inactivation and the development of soft tissue sarcoma.[5,9] However, although p53 inactivation and development of glioma are related, other biological molecular events, e.g. PTEN mutation, p16 inactivation, and epidermal growth factor receptor amplification, are also involved.[10,15] Indeed, p53 mutations are significantly less frequent in primary glioblastoma than in secondary glioblastoma.[17] Moreover, the

coexistence of several genetic mutation in glioblastoma[13] suggests that whereas a single mutation may suffice for the development of soft tissue sarcoma, this is not true for gliomas.

The present study showed that the SNP309 genotype is involved in the attenuation of MDM2 protein expression in glioma tissues but has no strong effect on the age at onset or histological classification. Overexpression of MDM2 induced by the SNP309 genotype does not appear to be critical in glioma tumorigenesis, although MDM2 attenuation via the p53 signal pathway may be involved in glioma progression.

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Commentary

The authors have reported that single nucleotide polymorphism in the promoter region of MDM2 (SNP309) is involved in the attenuation of MDM2 protein level

but has no significant effect on glioma tumorigenesis. MDM2 is a negative regulator of p53 that is mutated in half of gliomas. P53 inactivation is an early event of glioma tumorigenesis. SNP309 is associated with MDM2 protein expression level in the onset age of several types of cancer. In this study, the SNP309 genotype in 254 patients with glioma and 50 healthy subjects was examined. It was shown that SNP309 affected MDM protein level, but no correlation was found between the expression of SNP309 and that of MDM2 and p53, and also between the SNP309 genotype and age at disease onset or the histological grade of glioma. Recently SNPs related to onset or progression have been studied in numerous diseases, but not in glioma. This study showed that SNP309 had an effect on MDM protein level, but did not show that SNP309 was associated with glioma tumorigenesis and p53. This finding suggests that glioma tumorigenesis is not affected by SNP309, but whether another SNP affects glioma tumorigenesis remains unknown. SNP study for glioma will be useful, because it can contribute information about the probability of developing glioma in the future. Although no association between SNP and glioma tumorigenesis was established, it is valuable to pioneer a new field in glioma research.

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MDM2 has been shown to be a key controller of p53 which is involved in the genesis of a significant number of gliomas. Moreover, a number of prior studies have demonstrated the importance of the SNP309 genotype in tumorigenesis both in sporadic tumors and in inherited disorders, such as Li-Fraumeni syndrome. Thus, a study of the role of SNP309 in primary glioma tissue is important. However, in this study by Tsuiki et al. in a population of Japanese patients with gliomas, no strong association of SNP309 genotype was noted either in the histological grade of the tumor nor in the age of onset of the diagnosis. This is an important piece of information in our continual increase of understanding of gliomagenesis. It will be important to confirm this finding in other populations as well.

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The authors have studied the role of the SNP309 genotype in a series of 254 Japanese patients harboring gliomas, and 50 healthy subjects. They show that patients homozygous for G/G have a higher expression of MDM2 protein by immunohistochemistry. However, there was no association between the G/G genotype and histological grade of tumor, disease onset or p53 gene mutation status. It is interesting that the rates of the SNP309 genotype in Japanese subjects differed from that reported in a series of Western subjects.

SNP309 is found in the promoter region of the human MDM2 gene. Its presence alters the binding of transcription factors and ultimate affects the expression of MDM2. The authors' data are convincing that MDM2 protein is upregulated by immunohistochemistry. It would have been nice to see confirmatory evidence of the same using Western blot analysis. Precisely why the upregulated MDM2 did not affect tumorigenesis is an interesting but unanswered question at this stage. Perhaps it is a matter of dosing of MDM2 which could be higher in the context of MDM2 gene amplification than it is in the presence of the SNP309 genotype that makes the difference. I congratulate the authors on their fine genetic analysis.

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Role of surgery for optic pathway/ hypothalamic astrocytomas in children

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Optic pathway/hypothalamic pilocytic astrocytomas in children are usually treated with chemotherapy following a surgical biopsy. In this report, we retrospectively considered the role of surgical intervention. In a series of 25 patients without neurofibromatosis type 1, the median age at initial treatment was 3.1 years (range, 0–15 years). Twenty cases were verified by histology, and five cases were diagnosed by MRI findings. Twenty-three patients received chemotherapy. All patients were alive at median follow-up of 66 months. Aims of surgery at the initiation of treatment were biopsy in 12 cases (1 stereotactic and 11 craniotomies) and debulking in 7 cases. The 11 open biopsies revealed pilocytic astrocytoma; however, noticeable complications occurred in five children after the biopsies. Review of preoperative MRIs showed that all had typical findings indicating pilocytic astrocytoma. The open biopsy offered no noteworthy benefit for the patients despite surgical risk and delay of chemotherapy. The extent of the seven resection surgeries was 70% or less removal, and postoperative adjuvant therapy was needed for six of the seven patients. The remaining six children who did not undergo surgery obtained remission with chemotherapy alone. After relapse in nine patients, 15 bulk-reduction surgeries were performed. Surgical resection was not curative in any patient. In five patients, mostly older children, cystic expansion of tumor was partially resected, resulting in additional remission. In conclusion, considering the risk of open surgery and the effectiveness of chemotherapy, the role of surgical intervention is restricted to bulk-reduction surgery only when it is inevitable, especially at relapse after chemotherapy.

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Keywords: biopsy, hypothalamus, optic pathway, pilocytic astrocytoma, surgical removal

Optic pathway/hypothalamic glioma is a rare brain tumor that occurs mostly in young children. Initial manifestations are usually serious visual disturbance, hypothalamic dysfunction including diencephalic syndrome, or both. Although in general this tumor is WHO grade I pilocytic astrocytoma, in some patients, particularly in very young populations, the optic pathway/hypothalamic pilocytic astrocytoma (OPHPA) may show an aggressive clinical course, including dissemination through the cerebrospinal fluid pathway, and these are a variant type known as pilomyxoid astrocytoma.[1,2]

The literature contains a number of discussions concerning notable progress in the treatment of OPHPA, especially focusing on chemotherapy and radiation therapy.[2–15] Neurosurgical management, which seems even now to offer major contributions to control of the tumor, has rarely been given attention.[14,16,17]

In the young population with neurofibromatosis type 1 (NF-1)–associated OPHPA, decisions to initiate chemotherapy are generally made without biopsy and are guided by ophthalmological and imaging examinations.[18,19] In cases of sporadic OPHPA in non-NF-1 patients, a biopsy or a partial resection by craniotomy to confirm histology remains the first mode of treatment.[3,14]

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In addition to cases requiring the histopathological diagnosis, certain cases refractory to chemotherapy, cases with a large mass causing obstructive hydrocephalus, or cases with cystic expansion compressing the optic pathway occasionally require surgical debulking during the long clinical course. This report reconsiders the role of surgical interventions for various stages of OPHPAs, excluding NF-1–associated tumors.

Materials and Methods

We retrospectively assessed a series of 25 consecutive patients who had a clinical diagnosis of a sporadic OPHPA from a review of clinical records since 1992, when high-resolution MRI became routinely available. We excluded NF-1–associated gliomas, single optic nerve gliomas, unilateral hypothalamic gliomas, and quiescent cases found in patients older than 15 years because these tumors have different natural histories and require dissimilar treatment strategies.[8,18]

Histology (pilocytic astrocytoma, including pilomyxoid type) was verified in 20 of the 25 patients, with 19 patients undergoing surgery at the initiation of therapy and another at relapse. The remaining five patients were diagnosed by pathognomonic radiological appearance and typical clinical manifestations. Fifteen of the 25 patients had newly diagnosed disease; the remaining 10 patients were referred to our hospital after a biopsy or at the time of relapse. The median ages of symptom onset and initial treatment were 1 year (range, 0–14 years) and 3.1 years (range, 0–15 years), respectively.

At the time of initial diagnosis of brain tumor, all cases, in retrospect, had a typical appearance suggestive of pilocytic astrocytoma on high-resolution MRI (Fig. 1A,B) and CT, located in the midline involving the optic pathway and hypothalamus. Although the majority of the 25 tumors appeared as apparently well-demarcated masses on MRI, two had a predominantly infiltrative pattern involving the whole optic pathway, including the bilateral optic nerves, chiasm, tracts, geniculate ganglions, internal capsules, and optic radiations. Contrast enhancement on MRI was present for the most part in all but one case; in this latter case, a large tumor (involving the chiasm, right optic tract, and bilateral hypothalamus and occupying the third ventricle) exhibited a scarce enhancement pattern. To resolve obstructive hydrocephalus, the tumor was subtotally resected and found to be pilocytic astrocytoma upon histological examination. The maximum diameters of the 25 tumors, encompassing globular masses but excluding the infiltrating part to the surrounding brain, ranged from 34 to 65 mm. No cases had dissemination at the time of diagnosis.

Initial manifestations and reasons for initiation of therapy were diverse. Fifteen (60%) of the 25 children had their initial symptom before 2 years of age. Twenty children had visual impairment at the time of correct diagnosis. The interval between onset of initial manifestation and diagnosis of brain tumor was longer than 2 years for seven children. Among them, five children who were younger than 3 years at diagnosis showed a long-term history of visual impairment without hypothalamic dysfunction that had not been recognized by their parents. In contrast, 9 of 10 infants presenting recognizable symptoms, including either pendular/fixation nystagmus or diencephalic syndrome such as emaciation, anorexia, and weight loss, had diagnosis without delay. Others were found with headache due to obstructive hydrocephalus, dwarfism, or precocious puberty or had tumors that were found incidentally. An 8-year-old patient whose tumor was found incidentally was initially asymptomatic, but the tumor grew during a 3-year observation period and caused obstructive hydrocephalus and a slight visual field defect. All the patients were therefore symptomatic at the time of initial treatment.

The aims of surgery, at the initiation of treatment, were biopsy (very limited resection) in 12 cases (1 stereotactic surgery and 11 craniotomies) and tumor debulking in 7 cases. If a typical low-grade astrocytoma was encountered during craniotomy and limited resec-

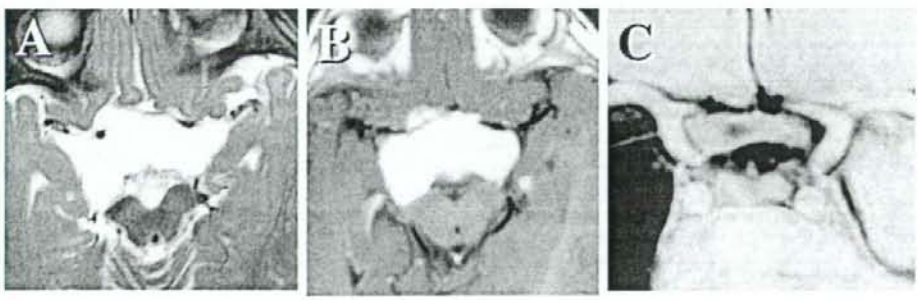

Fig. 1. MR images of a 1-year-old patient demonstrate typical appearance of pilocytic astrocytoma. T2-weighted axial image (A) shows a high-signal intensity suprasellar mass that is homogeneously enhanced with gadolinium contrast on T1-weighted image (B). After six cycles of chemotherapy, the tumor almost completely disappeared on usual MR images; however, a coronal image of three-dimensional MR cisternography (C) depicted a tiny residual tumor within the right side of the chiasm.

tion was then performed, it was evaluated as a "biopsy" case in this report. Partial removal was defined as less than 90% resection. These 19 patients underwent surgery for progressive symptoms or progressive tumor growth. In six patients, the decision to initiate chemotherapy was made without biopsy and was guided by serial MRI examinations. In nine patients with relapse, a total of 15 salvage surgeries were performed. In the present series, 21 (62%) of 34 various craniotomies were performed by the senior author (Y.S.). The surgical procedures applied were pterional frontobasal transsylvian, transcallosal interseptal, transcallosal trans-foramen of Monro, frontal transcortical, and interhemispheric trans-lamina terminalis approaches.

Twenty-three (92%) patients were treated with chemotherapy, and six patients (24%) with a relapsing tumor after chemotherapy received radiation therapy. The remaining two patients underwent surgical resection alone without adjuvant therapy. Generally, three chemotherapeutic regimens were used: cisplatin with vincristine,[5] carboplatin with vincristine, and temozolomide.

Neurological and radiological examinations were performed before and after surgery. Assessment of overall response was based on tumor evaluation by MRI and interpreted according to the Response Evaluation Criteria in Solid Tumors (RECIST).[20] Complete surgical resection was defined as no visible tumor found on high-resolution postsurgical MRI and was not based on surgical record.

Results

Outcome of Patients

All 25 children tolerated the various therapies well and were alive at median follow-up of 66 months. Among them, only one patient achieved a completely tumor-free status of 9-year duration, after spontaneous complete involution on serial MRI observation. Final outcome of the remaining 24 patients could not be determined due to the short period of observation. At the final observation, Karnofsky performance status was better than or equal to 70% in 20 patients. All children, except one who was completely blind at birth, retained functional vision in at least one eye.

Initial Therapy in Cases with Surgical Biopsy or Resection

At the initiation of treatment, 19 patients underwent surgery, including stereotactic biopsy in 1 case, craniotomy biopsy (limited resection) in 11 cases, and debulking surgery in 7 cases. No endoscopic biopsy was applied in this series. Five children received a ventriculoperitoneal shunt for obstructive hydrocephalus. Because of the location of a tumor at the bottom of the third ventricle, endoscopic third ventriculostomy was not available for any patient.

Eight of 12 biopsies were performed at a previous hospital, with these children then referred to our institution. The 12 biopsies revealed a histological diagnosis of WHO grade I pilocytic astrocytoma, including pilomyxoid type in seven patients. There were no cases of anaplastic tumor. One tumor was initially diagnosed as fibrillary astrocytoma, but pathology review confirmed pilocytic astrocytoma. Because 7 of these 11 children were younger than 4 years, precise assessments of their visual function (including visual field evaluation and minimal change of cognitive function) were not possible. Noticeable postsurgical symptomatic complications were observed in five patients. One patient had deterioration of cognition after consciousness disturbance for 2 weeks. One had worsened bitemporal hemianopsia. One had postsurgical epileptic seizures. One had moderate, but transient, hemiparesis. In two infants who underwent a frontal interhemispheric approach, postsurgical MRI examinations showed medial frontal malacia in the rectal and cingulate gyri on T2-weighted images; one was symptomatic (consciousness disturbance for 2 weeks), and the other was asymptomatic. In another child, a small cerebral infarction was found due to a perforating artery injury originating from the middle cerebral artery, although this child seemed asymptomatic.

For initial treatment, bulk-reduction surgery by craniotomy was performed in seven children with large-volume tumors (Table 1). The senior author (Y.S.) performed two of these craniotomies. Although obstructive hydrocephalus in two children resolved after craniotomy, the extent of resection surgeries appeared to be insufficient, resulting in removal of 70% or less of the tumor volume. Following the surgery, six patients received adjuvant chemotherapy. One child received radiation therapy at 6 years of age, 4 years after initial surgery, due to an aggressive relapse after cycles of chemotherapy with carboplatin and vincristine. As a result, benefits of the first resection surgery were obscure for the seven children; nevertheless, postsurgical complications were considerable, as shown in Table 1.

Initial Therapy in Cases without Biopsy

Given patient age, initial manifestations, location of tumor, and preoperative radiological appearance, the decision to initiate chemotherapy was made without biopsy and was guided by serial MRI in six patients with typical features of OPHPA at initial diagnosis. All these patients had their disease newly diagnosed at Hokkaido University Hospital. They successfully obtained a durable remission after either six or eight cycles of chemotherapy using cisplatin and vincristine, although no patients achieved a complete response. One patient underwent unilateral optic nerve decompression during first-line chemotherapy. Two patients who had a large mass after completion of initial chemotherapy continually received second-line chemotherapy using either carboplatin/vincristine or temozolomide. Two of the six patients showed relapse: one patient, after a 34-month remission, was treated with temozolomide; the second patient, after a 65-month remission, required subsequent irradiation and then salvage surgery for bulk reduction.

Table 1. Results of bulk-reduction surgery at initial treatment

Patient Age	Route (Approach)	Postsurgical Complications	Brain Tissue Damage	Extent of Surgery (Volume)
2 years	Frontal interhemispheric	Epilepsy	Mesial frontal lobe	<50%
1 year	Anterior transcallosal	Cerebral salt wasting syndrome, slight right hemiparesis, possible cognitive deterioration	Fornix, anterior commissure, right deep frontal, hypothalamus	<50%
3 years	Right frontal transcortical	Hypothalamic dysfunction, body temperature dysregulation, mental deterioration, worsened vision	Right frontal lobe, hypothalamus, visual pathway	~70%
3 years	Frontal interhemispheric	Panhypopituitarism, epilepsy, right visual loss	Optic nerve, chiasm, hypothalamus, stalk, mesial frontal lobe	<50%
3 years	Anterior transcallosal through foramen of Monro	None	None	<50%
7 months	Frontobasal transsylvian	None (total blindness prior to surgery)	Resection of right optic nerve	<50%
5 months	Frontobasal transsylvian	Right visual loss	Right optic nerve and chiasm	<50%

At median follow-up of 47 months, all six of these children were alive with stabilized residual mass on MRI.

Fig. 1 shows representative MR images for a 1-year-old patient who presented with diencephalic syndrome, progressive emaciation, and severe visual impairment. This child was given chemotherapy without biopsy. During the period of chemotherapy, the tumor had gradually shrunk toward the optic chiasm and finally disappeared almost completely on usual MR images. However, a coronal image of three-dimensional MR cisternography (three-dimensional constructive interference in steady-state MRI) showed a tiny residual tumor in the right side of the chiasm. The patient's disease had been stable for 73 months with slightly improved visual acuity. For this child, either biopsy or partial resection would have resulted in additional visual impairment.

OPHPA occasionally infiltrates the optic nerve in the optic canal and orbit. In our series, only 3 of the 25 cases presented with optic nerve invasion in remarkably expanded optic canal(s). Fig. 2 shows a coronal image of a swollen optic nerve in the right optic canal. This patient had count-finger visual acuity on the right and 2/200 on the left. The right vision occasionally deteriorated to the level of light perception, especially when the patient had a high fever. Because of the deterioration of visual acuity during first-line chemotherapy, the optic canal was unroofed by an emergent craniotomy to decompress the affected nerve without tumor resection. Postoperatively, the patient's visual acuity was preserved and 3 years later was 4/200 on the right and hand movement to 2/200 on the left. After cycles of chemotherapy, the swollen optic nerve gradually shrank.

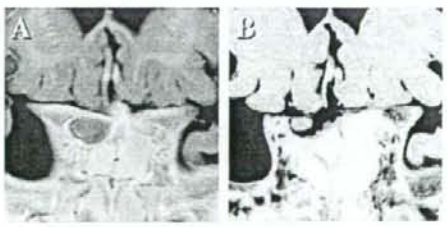

Fig. 2. A coronal image shows a swollen optic nerve in the right optic canal (A; multiple planner reconstruction image). Due to deterioration of visual acuity, the optic canal was unroofed to decompress the affected nerve. After cycles of chemotherapy, the optic nerve gradually shrank (B; three-dimensional MR cisternography).

Salvage Surgery for Relapse

Nine children underwent salvage surgery for relapse: 12 partial resections, 2 gross total removals, and 1 cyst puncture by image-guided stereotactic method. The salvage bulk-reduction surgery was performed to partially remove a relapsing tumor after prolonged chemotherapy and prior to second-line chemotherapy, to reduce a large mass prior to planned radiation therapy to solve obstructive hydrocephalus, or to remove the wall of the expanding cyst(s). Five patients underwent salvage surgery once, and three patients underwent such surgery twice. Another child, who had previously received various chemotherapies and radiation, underwent partial removal twice and then gross total removal twice.

Regarding postsurgical quality of life, complete surgical resection could not be achieved in any patient due to the invasive nature of the tumor into the optic pathway and the bilateral hypothalamus. Median follow-up for the nine patients was 128 months (range, 42–174 months), and all were alive at the final observation.

Fig. 3 shows a large pilocytic astrocytoma in a 33-month-old patient who had been given cycles of chemotherapy following initial biopsy when she was 6 months old. Because the second partial removal was insufficient, the patient was referred to our institution. To further reduce the large volume, a radical resection was performed, leaving the tumor margin intact to preserve the residual hypothalamic function and very poor

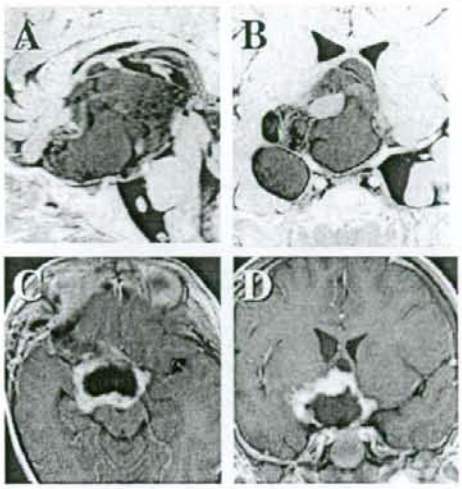

Fig. 3. A progressively growing pilocytic astrocytoma in a 2-year-old child who underwent long-term chemotherapy and partial tumor removal twice (A and B). Through the frontobasal transsylvian route, a radical third resection was performed, leaving the tumor margin intact (C and D). Tumors of this size involve the circle of Willis, including its numerous perforators.

vision of the left eye. Maintenance chemotherapy using temozolomide is ongoing at the time of this writing. Relapsing tumor of a similar size was seen in three children, and all involved the circle of Willis, including its numerous perforators, as well as the optic pathway and the hypothalamus. In these cases, the risk posed by sufficient bulk-reduction surgery that was required prior to either alternative chemotherapy or radiation therapy was extremely high, although we fortunately did not observe any unacceptable postsurgical sequelae.

Spontaneous involution after partial resection was observed in three patients. In the case shown in Fig. 4, the mass filling in the third ventricle was selectively removed, leaving a part of the tumor infiltrating the chiasm and the hypothalamus, because the patient still retained good vision and pituitary function without diabetes insipidus. Although the selective excision was technically hard, intraoperative observation revealed that the proliferating part of a relapsing tumor was very soft and easily resectable, while the tumor infiltrating the brain tissue was relatively firm, probably due to a mixed gliofibrous component.

For one child who had received chemotherapy, radiation therapy, and partial resections with transection of the left optic nerve over a period of 8 years, a radical total resection of a relapsing tiny tumor adherent on the chiasm was attempted. The result of surgery was evaluated as a gross total removal on MRI. Three years later, the tumor eventually recurred on the left optic tract and was radically resected again. This patient had been receiving maintenance chemotherapy using temozolomide, and he was tumor free on MRI for an additional 2 years, maintaining half nasal-side vision of the right eye. Whether this final surgery could lead to a disease cure is not clear because of the short observation period.

Multi- or single-cystic expansion of the tumor was observed in five older patients after a long disease course, with enlargement of tumor cyst(s) occurring at 4, 8, 10, 15, and 18 years of age. Four of the five patients underwent partial resection of the cyst wall by craniotomy, and the fifth patient underwent an image-guided stereotactic puncture of a subcutaneous reservoir. Only one experienced a further relapse of multiple cysts and was treated by craniotomy again. These surgical treatments resulted in further remission in all five patients, and three resulted in improvement of deteriorating vision. Among them, a spontaneous complete involution of the residual enhancing mass was observed in the child who received stereotactic puncture of the cyst. Pathological examinations showed predominantly degenerative changes of pilocytic astrocytoma, in which the index for Ki-67 staining was less than 1%. Fig. 5 shows a multicystic expansion of a pilocytic astrocytoma. The volume of tumor parenchyma enhanced with gadolinium contrast

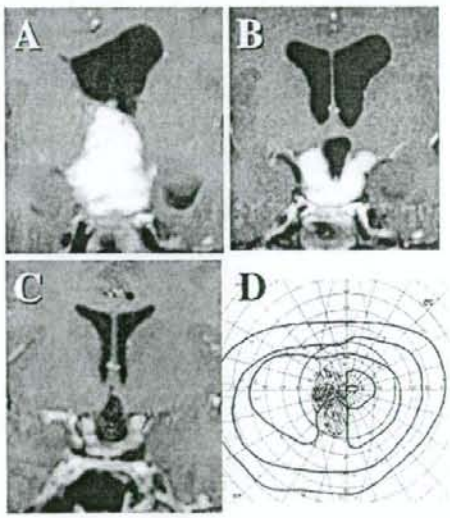

Fig. 4. A relapsing tumor (A) in a 7-year-old boy, who had received chemotherapy for 7 years following a partial resection. MR image shows a homogeneous tumor, but the tumor infiltrating the chiasm and the hypothalamus was relatively firm, and only the soft mass filling in the third ventricle was selectively resected (B). Five years later, when the patient was 13 years old, the residual tumor had spontaneously shrunk, and visual function was preserved (C and D).

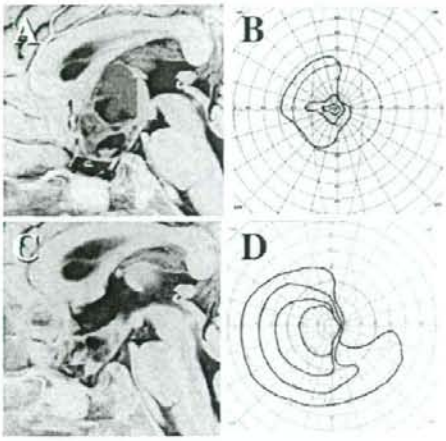

Fig. 5. A multicystic expansion of a pilocytic astrocytoma after 9-year remission following initial chemotherapy and radiation therapy (A). The visual function was deteriorated (B). A partial removal of the cyst wall by a craniotomy achieved collapse of most of the cysts (C) and improvement of vision (D).

had been stable. The visual function of this 10-year-old patient was rapidly deteriorating. Partial removal of the cyst wall by craniotomy resulted in collapse of most of the cysts and improvement in the patient's vision. A selective resection of cystic walls preserving the remaining optic pathway always requires precise presurgical MRI investigation with three-dimensional MR cisternography and careful surgical planning.

Discussion

All 25 children tolerated the various therapies well, and all were alive at the time of final observation. Among them, only one patient definitely achieved a tumor-free status. The long-term final outcome of these patients will be clearer 10 or more years after this report. Therefore, we here focus on the efficacy of the surgical interventions.

Biopsy at the Initiation of Therapy

In 1995, Sutton et al.[14] reported the long-term outcome of hypothalamic/chiasmatic astrocytomas in children treated with conservative surgery. In their series, all patients who had globular suprasellar masses without involvement of optic nerves or optic radiations underwent surgical exploration. The goal of this surgery was primarily to establish a histological diagnosis, and if a typical low-grade astrocytoma was encountered, a biopsy and limited resection were performed. Large masses obstructing the foramen of Monro were debulked to relieve ventricular obstruction, but generally no attempt at gross total excision was made. This concept may have been widely accepted as a standard surgical strategy for OPHPA at initial treatment.[3,21]

Currently, OPHPA in children with usual clinical and radiographic appearance using modern MRI technique can be more correctly diagnosed without surgical biopsy. The majority of such patients respond to platinum-based chemotherapy.[1–7,9–11] Serious visual dysfunction can be improved by chemotherapy, and a chemotherapy-first strategy can preserve the intellectual outcome of patients who thereby avoid the need for radiotherapy.[22,23] In our series, 11 biopsies (limited resections) by craniotomy in fact caused remarkable complications related to surgical procedure. We speculate that these were attributable to incorrect preoperative diagnosis or insufficient experience of the surgeon. For example, two young children had a preoperative diagnosis of craniopharyngioma; however, pilocytic astrocytoma was suggested by frozen section during the craniotomy. In these children, a bifrontal interhemispheric approach by a large craniotomy was used; nevertheless, the surgery produced unnecessary complications. In contrast to chemotherapy, the result of surgical intervention depends on the surgeon's skill and experience. The benefit of surgical biopsy at initiation of therapy may therefore be ambiguous considering surgical morbidities, cost, and delay of chemotherapy. Silva et al.[11] treated 14 young children, including four patients after endoscopic biopsy and five patients without biopsy, and recommended chemotherapy as a primary treatment for optic pathway/hypothalamic gliomas.

Gliomas in similar locations, such as NF-1–associated gliomas, single optic nerve gliomas, hypothalamic hamartomas, and unilateral hypothalamic gliomas, require a treatment strategy distinct from that for OPHPA. Excluding these instances by MRI examination, the vast majority of gliomas involving the optic pathway and bilateral hypothalamus in children are pilocytic astrocytomas.[8,14,24] Other tumors in the same region, however, may mimic OPHPA and would necessitate different therapeutic approaches. In addition to routine imaging studies and endocrinological assessments, examinations of tumor markers in the serum and cerebrospinal fluid and high-resolution MR images, such as MR cisternography or multiple planner reconstruction image, should suitably assist the diagnosis, to rule out craniopharyngioma, various germ cell tumors, Langerhans cell histiocytosis, hypothalamic hamartoma, diffuse astrocytoma, or ganglioglioma. In some cases, surgical biopsy is indispensable to confirm histological diagnosis. In some instances, image-guided stereotactic biopsy or endoscopic biopsy may be feasible and valuable. These procedures carry some risk, and difficulty may be experienced in small children without dilatation of lateral ventricles.

Pilomyxoid astrocytoma, an infantile variant with known aggressive potential, may be more susceptible to chemotherapy and exhibit more typical features on MRI compared with classical pilocytic astrocytomas found in older children,[2,4,6–10,15,21,24] given that children younger than 1 year have a higher risk for tumor progression than do older children.[6,8,15,17] The surgical risk of cran-

iotomy for very small children is clearly high. Furthermore, a combination of surgical operation and histological examination may delay initiation of chemotherapy. Moreover, surgical removal might introduce tumor cell seeds into the cerebrospinal fluid pathway. There may be no place for surgical exploration in the treatment of young children, except for endoscopic biopsy.

Partial Resection at the Initiation of Therapy

In addition to the use of biopsy for diagnosis, some investigators have advocated resection for large tumors, and certain children can obtain long-term amelioration by initial surgical resection alone.[16,17] In 2002, Steinbok et al.[25] reported surgical results for 18 chiasmatic-hypothalamic astrocytomas; eight patients had subtotal resections, six had partial resections, three had limited resections, and one had no surgery. Fewer complications were associated with the limited resections, especially with respect to hypothalamic dysfunction. There was no correlation between the extent of resection and the time to tumor progression. The chiasmatic-hypothalamic tumors caused more morbidity than did the chiasmatic tumors, and radical resections did not prolong time to progression compared with more limited resections. The authors concluded that if surgery is performed, it may be appropriate to do a surgical procedure that strives only to provide a tissue diagnosis and to decompress the optic apparatus and/or ventricular system.

We agree with the conclusion of Steinbok et al.[25] Selective decompression of the optic apparatus, however, appeared to be difficult. Precise estimation of visual dysfunction as a consequence of partial resection is difficult to nearly impossible, especially in young children. Surgical morbidity in the previous reports might have been underestimated with respect to visual function in children. In addition, as demonstrated in Fig. 1, if the tumor is located mainly in the chiasm, a partial excision of the tumor will injure the visual pathway.

Concerning the complications and invasiveness of such debulking surgery, decompression of the ventricular system by a partial resection can be replaced with a ventriculoperitoneal shunt, with or without endoscopic septotomy. Only when chemotherapy fails to induce or maintain remission should salvage debulking surgery be planned.

Salvage Resection Surgery

Chemotherapy is increasingly being used and is occasionally curative, and it provides a stabilizing role in most cases.[3,6,8,9,11] Following initial induction chemotherapy, even if it was effective and given for a long period, many children with OPHPA experience tumor relapse. The second-line treatment may be alternative chemotherapy, and radiation therapy might then be considered at further progression.[6] Because the long-term effectiveness of conventional fractionated radiation therapy, including recent stereotactic techniques, is superior to that of chemotherapy,[3,26–28] radiation therapy is available for older children with a localized relapse. However, some OPHPAs are "surgically amenable" in a subset of patients with recurrent disease.[14,17]

It is known that optic gliomas in non-NF-1 patients often regress spontaneously.[13,17,29] If most pilocytic astrocytomas have a limited time span for growing and lower age is a worse prognostic factor,[8,21,30] a partial resection to ameliorate symptoms or to reduce mass effect of a growing tumor may be worthwhile. In our series of patients, spontaneous involution after partial resection or cyst puncture of a relapsing tumor was observed in four patients. This result may warrant a salvage maximal (partial) excision for relapsing tumor with parenchymal growth, especially in older children.

Radical Surgery and Complication

Radical surgery for patients with OPHPA carries the risk of damage to the hypothalamus, visual apparatus, and vascular structures.[17] In addition, no complete surgical resection could be achieved when the functional outcome was seriously considered.[2,14,24] Neurosurgeons, however, seldom have the opportunity to operate on OPHPA, which is an uncommon childhood brain tumor. In addition, the surgical strategy and technique are extremely complex. In our series of patients, the complication rates from biopsy and bulk-reduction surgery at the initiation of therapy seemed to be unexpectedly high compared with literature reports.[2,3,11,14,17,21] Definitive permanent deficits occurred in two children after 11 open biopsies and in four children after 7 bulk-reduction surgeries. Few of these complications, however, resulted from the surgeries performed by the senior author, suggesting an effect of surgeon experience.

It is of note that results of such surgical excisions may vary and that the results greatly depend on the experience of the neurosurgeon. Although OPHPA should be operated on by an experienced surgeon, results will vary with the specific conditions in each case. Radical surgical resection of OPHPA will therefore generally be offered only when the tumor has progressed despite feasible chemotherapy or, in certain cases, radiation therapy.

Partial Removal for Cystic Expansion

Cystic tumor expansion without parenchymal growth occurred mostly in older children. The formation of cysts may be a consequence of tumor degeneration and may occur prior to spontaneous involution, as observed in cases of vestibular schwannoma. The growing cyst (containing proteinaceous fluid) appeared to be refractory to both chemotherapy and radiation therapy. An intended nonaggressive partial resection of cyst wall(s) or stereotactic puncture can ameliorate progressive visual disturbance and produce a certain term of remission.

Optic Nerve Decompression

OPHPA occasionally involves the optic nerves in the optic canal. The swollen optic nerve expands the bony optic canal, especially in very young children (younger than ~4 years of age) and may result in entrapment neu-

ropathy of the optic nerve itself. To our knowledge, no report has described the efficacy of optic nerve decompression for such cases. Although we had a solitary case of successful decompression in the present series, this surgical procedure may be applied to rescue very poor vision caused by optic nerve invasion by tumor cells.

In conclusion, to treat OPHPA in young children, surgical biopsy appears to be dispensable for clinically or radiologically typical cases. A curative resection is rarely achieved when the functional outcome of patients is seriously respected. The role of surgical intervention may be restricted to bulk-reduction surgery only when it is inevitable. However, during the long clinical course of OPHPA in children, especially at relapse, both chemotherapy and radiation therapy have to be selected considering a variety of available surgical treatments with neurosurgeons who have profound experience with this unique tumor.

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