

Ganglion Cell Tumors

Sung-Hye Park and
Harry V. Vinters¹

Department of Pathology, Ilsanpaik Hospital, Inje University, College of Medicine, Koyang, Korea;
¹Department of Pathology Laboratory Medicine (Neuropathology), Brain Research Institute and Mental Retardation Research Center, UCLA Medical Center, Los Angeles, California, U.S.A.

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Corresponding Author

Sung-Hye Park, M.D.
Department of Pathology, Ilsan Paik Hospital, Inje University College of Medicine, 2240 Daewha-dong, Ilsan-gu, Goyang 411-706, Korea
Tel: 031-910-7141
Fax: 031-910-7139
E-mail: sunghye@ilsanpaik.ac.kr

Background : In ganglion cell tumors, immunohistochemical characteristics and malignant changes of neuronal cells and the usefulness of the MIB-1 (Ki67) indices for grading ganglion cell tumors and abnormalities of the adjacent nonneoplastic cortex have been issued. **Methods :** The clinicopathologic features of 34 surgically resected ganglion cell tumors (32 gangliogliomas and 2 gangliocytomas) were retrospectively analysed, and immunohistochemical characteristics and malignant changes of neuronal cells and the usefulness of the MIB-1 (Ki67) indices for grading ganglion cell tumors and abnormalities of the adjacent normal cortex were investigated using various immunohistochemical studies. **Results :** According to the Daumas-Duport grading system, there were 24 (70.6%) grade II, 8 (23.5%) grade III, and two (5.9%) grade IV cases. Malignant transformation was present only in the glial (7 cases) or both glial and neuronal (3 cases) components. The MIB-1 indices were statistically significant ($p < 0.001$): grade II was 0.0-1.05% ($0.27 \pm 0.3\%$), grade III was 0.8-8.02% ($2.8 \pm 3.2\%$), and grade IV was 3.0-4.99% (3.99 ± 1.0). Anaplasia and MIB-1 positivity was observed among the neurons in the three cases. Perikaryal cytoplasmic expression or surface punctate accentuation of synaptophysin were noted only in the neoplastic neurons in some cases. Fifteen out of 20 cases, which included the nonneoplastic cerebral cortex, displayed mild cortical dysplasia (microdysgenesis). **Conclusions :** The neuronal component also showed malignant transformations with proliferating activity. In our study, synaptophysin-immunoreactive patterns of neoplastic neurons were unique. The MIB-1 indices were helpful for grading ganglion cell tumors. Only mild cortical dysplasia was present in the normal cortex adjacent to the tumor.

Key Words : Neoplasms, Neuroepithelial-Immunohistochemistry-Ki-67 Antigen-Synaptophysin

Ganglion cell tumors occur rather infrequently and account for 0.4%¹ to 1.3%² of all adult brain tumors, and 4.3%³ to 10.7%⁴ of children's brain tumors. By definition, gangliogliomas are mixed tumors of neoplastic, mature neuronal cells and neoplastic glial cells.⁵ Gangliocytomas are pure neoplastic, mature ganglion cell tumors.⁵ Usually, the histopathological grading of the gangliogliomas depends on the glial component, and the neuronal component is almost always benign. Over 90% of ganglion cell tumors are benign and frequently associated with medically intractable seizures. Cortical architectural abnormalities were suggested as the focus of seizures.⁶ The neoplastic nature and the possibility of malignant progression of the neuronal component are still uncertain.⁷

Here, we investigate any unique immunohistochemical features of the neuronal component for discriminating the neoplastic ganglion cells from normal entrapped neurons, the usefulness of the MIB-1 indices for grading ganglion cell tumors and abnormalities of the nonneoplastic cortex adjacent to the tumor.

MATERIAL AND METHODS

Among thirty-nine patients with ganglion cell tumors treated at the UCLA Medical Center from 1969 to 1996, 34 resected cases were reviewed clinicopathologically and retrospectively. The operation-report and post-operative imaging studies defined the extension of resection. Imaging studies including magnetic resonance (MR) imaging, computed tomography (CT), and cerebral angiography were reviewed.

Tissues available ranged from biopsies to lobectomies. We observed the type of glial component, the presence of binucleate neurons, perivascular inflammation, calcification, necrosis, mitoses, endothelial proliferation, eosinophilic granular body formation, Rosenthal fibers, leptomeningeal involvement and Scherer's secondary structures. New World Health Organization classification regards the ganglioglioma as a grade 1 tumor, which has a low or uncertain malignant potential or borderline malignancy and a grade 3 malignant counterpart, which even-

Table 1. Antibodies used in immunohistochemical study

Antibody to	Clonality	Source	Dilution	Control tissue
Synaptophysin	Monoclonal	DAKO	1:200	Brain
NSE	Polyclonal	DAKO	1:200	Brain
SMI 31 (NF)	Monoclonal	Sternberger	1:1,000	Brain
Chromogranin A	Polyclonal	DAKO	1:200	Adrenal medulla
GFAP	Polyclonal	BioGenex	Prediluted	Brain
MIB-1 (Ki-67)	Monoclonal	BioGenex	1:40	Carcinoma

NSE: neuron specific enolase, NF: neurofilament, GFAP: glial fibrillary acidic protein.

tually may lead to the histological features of glioblastoma.⁵ We used the Daumas-Duport grading system to classify the grading of the glial component. In addition, we looked for abnormalities of the non-neoplastic brain tissue adjacent to the tumor *i.e.*, cortical architectural abnormalities, mesial temporal sclerosis and neuronal heterotopia.

Using avidin-biotinylated immunoperoxidase methods, immunohistochemical stains were carried out with antibodies for synaptophysin (DAKO, Netherland), neuron specific enolase (NSE, DAKO, Netherland), neurofilaments (Sternberger), chromogranin A (DAKO, Netherland), glial fibrillary acidic protein (GFAP, BioGenex, California, U.S.A.) and MIB-1 (Ki-67, BioGenex, California, U.S.A.) (Table 1). Appropriate positive and negative controls were performed in each case (Table 1). For MIB-1 indices, on each immunostained slide, 1,000 neoplastic cell-nuclei were counted in the most prominently immunolabelled region, irrespective of tumor cellularity, using a 200X objective. Only distinct nuclear staining was interpreted as positive. In each case, the MIB-1 labeling index (the number of MIB-1 positive nuclei/1,000 tumor cells counted) was calculated.

RESULTS

Clinical data

The median age of the 34 patients was 18 years (range: 8 months to 64 years). Eighteen patients were female, and 16 were male. The median duration of symptom awareness prior to diagnosis was 5 years prior to diagnosis (range: 1 month to 30 years). Twenty-seven of the 34 patients (79.4%) experienced seizures. Five patients experienced headaches, one had blurry vision and papilledema, one had aphasia, and one had dyspnea. The median tumor size was 3 cm (range: 1 to 10 cm).

All patients were treated surgically. Twenty-one patients (61.8%) underwent gross total resections, and 13 patients

(38.2%) were treated with subtotal resections. Of the thirteen patients who were treated with subtotal resections, six were treated with adjuvant therapy. Two patients were treated with chemotherapy, two were treated with radiotherapy, one patient received both chemotherapy and radiotherapy, and one patient was treated with acupuncture. The tumors were located in the temporal lobe in 24 cases (70.6%), the frontal lobe in five (14.7%), and the occipital lobe in two cases (5.9%). One case each was located in the parietal lobe, cerebellum, and brainstem. The 4-year actuarial survival of all 34 patients was 75%. There was an apparent prognostic difference in overall survival between the grade II and grade III groups. However, we could not obtain great prognostic differences between the grade III and IV groups because the number of grade IV was too small (only two cases).

Preoperative imaging studies or their reports were available for 32 patients. Many of the tumors were centered peripherally, with cortical or subcortical involvement. Precontrast CT findings included a hypodense, less likely to be isodense, tumor that was usually relatively well defined. 20 cases (62.5%) were enhanced on CT scans. Six tumors were calcified. On MR, most of the ganglion cell tumors in this series was hypointense to the brain on T1 weighted imaging, although a few were isointense to the brain. On T2W and proton density sequences, the tumors were hyperintense to the brain in all cases. Gadolinium enhancement was apparent in 65% (11 of 17) of the cases. Fifty-eight percent of the tumors were partially cystic. Eight tumors showed significant perilesional white matter edema, 50% of which were either grade III or IV ganglion cell tumors. Cerebral angiography most commonly showed avascular mass effect with a few of the small tumors having normal angiograms. Only one tumor, an anaplastic ganglion cell tumor, measuring over 10 cm in size, demonstrated hypervascularity.

On early (mean=4 days) postoperative CT or MR scans, 8 of 32 patients scanned showed residual tumors, all having undergone subtotal tumor resections. On delayed (mean=38 months) postoperative scans, 7 of 28 patients scanned had tumors, 5 of

whom had had residual tumors on their early scans. The other two patients had anaplastic gangliogliomas. In 6 of the 7 patients, there were interval tumor growths, and one tumor was stable.

Histopathologic findings

All gangliogliomas had neuronal and glial cell components: On HE stained sections, Nissl substance was usually definite but variably prominent. Binucleate neurons were found in 61.8% (21/34 cases) of ganglion cell tumors, but they were very rarely

seen in individual cases. There were pleomorphic or bizarre neurons with mitotic figures in two grade III cases and in one case of grade IV ganglion cell tumor, which were immunoreactive for MIB-1, synaptophysin and NSE (Fig. 1).

The glial component was astrocytic in 24 cases, mixed oligoastrocytic in 9 cases, and oligodendroglial in one case. Among the astrocytic tumors, 2 were pilocytic and 2 were astroblastomatous. Two cases fulfilled the criteria for being a glioblastoma, and the remaining cases were conventional astrocytic tumors. Twenty-four cases were grade II, 8 cases were grade III, and two cases were grade IV.

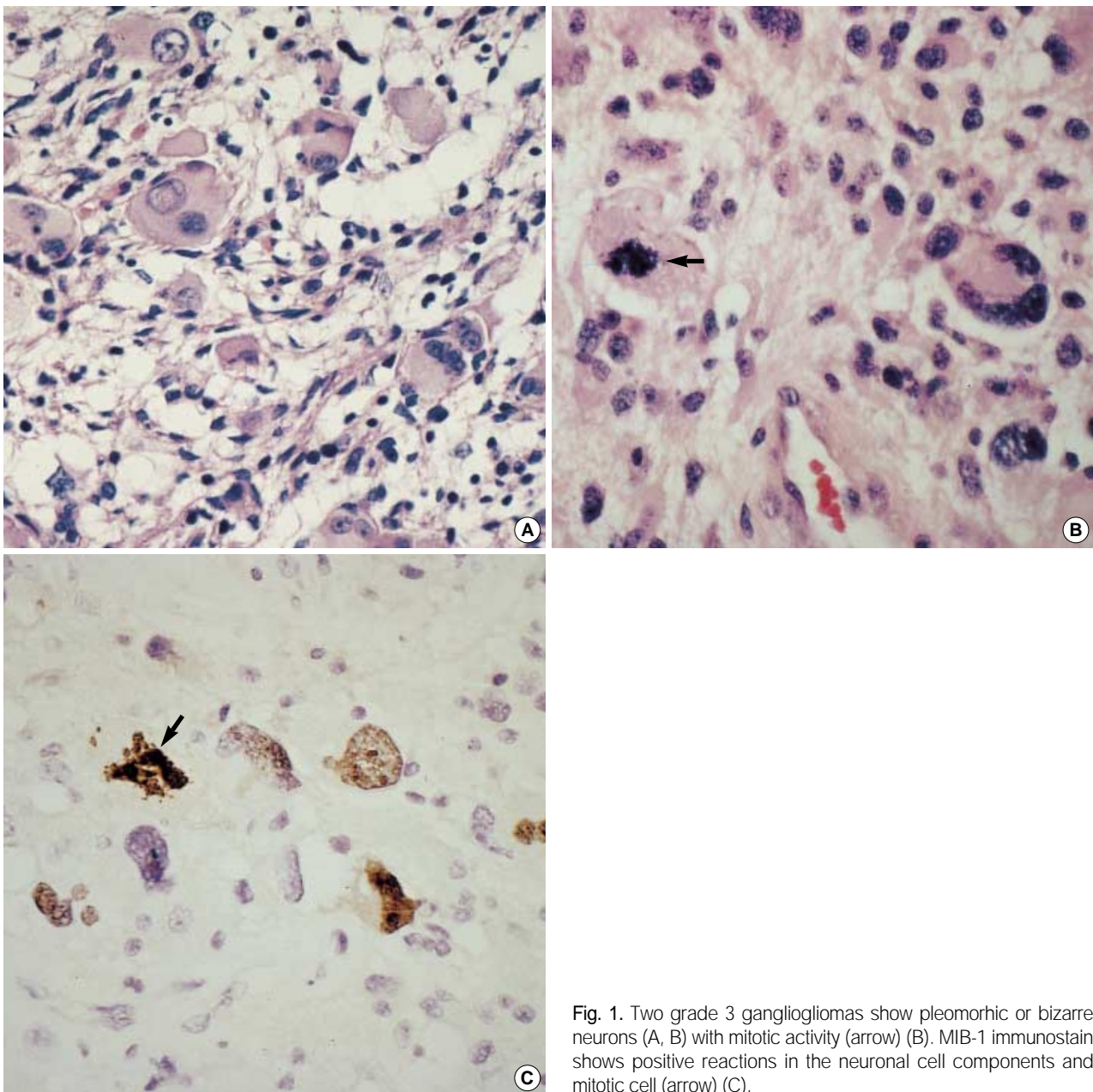


Fig. 1. Two grade 3 gangliogliomas show pleomorphic or bizarre neurons (A, B) with mitotic activity (arrow) (B). MIB-1 immunostain shows positive reactions in the neuronal cell components and mitotic cell (arrow) (C).

In 7 cases (20.6%), there was leptomeningeal involvement of the tumors (3 were grade III and four were grade II). In one case that was otherwise grade II, there were Scherer's secondary structures as judged by subpial collections of tumor cells. Calcifications were seen in 17 cases (50%) and perivascular lymphoplasmacytic infiltration was noted in 22 cases (64.7%). In two cases, calcification was massive, and in one case, there was diffuse and clustered lymphoplasmacytic cell infiltration in the tumor. Rosenthal fibers were seen in three cases, and eosinophilic granular bodies were observed in 10 cases (29.4%).

In 20 cases, cortical tissues were included in the resected brain; and among them 15 cases (75%) showed microdysgenesis (mild cortical dysplasia), such as laminar disorganization, some scattered disoriented and dysmorphic neurons, overcrowded and/or sparse areas of neurons and scattered neuronal heterotopia in the molecular layer or in the deep white matter. There were no cases with mesial temporal sclerosis. In all 15

cases, we found Chaslin's gliosis.

Immunohistochemical findings

In the normal brain tissue, synaptophysin immunostaining showed diffuse granular positive pattern in the neuropils and negative in normal neuronal cell body and their cytoplasmic membrane (Fig. 2A). However, the neoplastic neurons showed three characteristic appearances: namely, they are cytoplasmic surface punctate (Fig. 2B), perikaryal cytoplasmic immunoreactivity (Fig. 2C), or both. The latter were neither homogeneous nor seen in all cases.

Anti-neurofilament antibody was found in all cases, but in variable amounts in each case. Some cases showed strong positivity mainly within the axons, and some cases were focally immunoreactive in the perikaryal cytoplasm of the neurons (Fig. 2D). NSE was expressed in the perikaryal cytoplasm of all

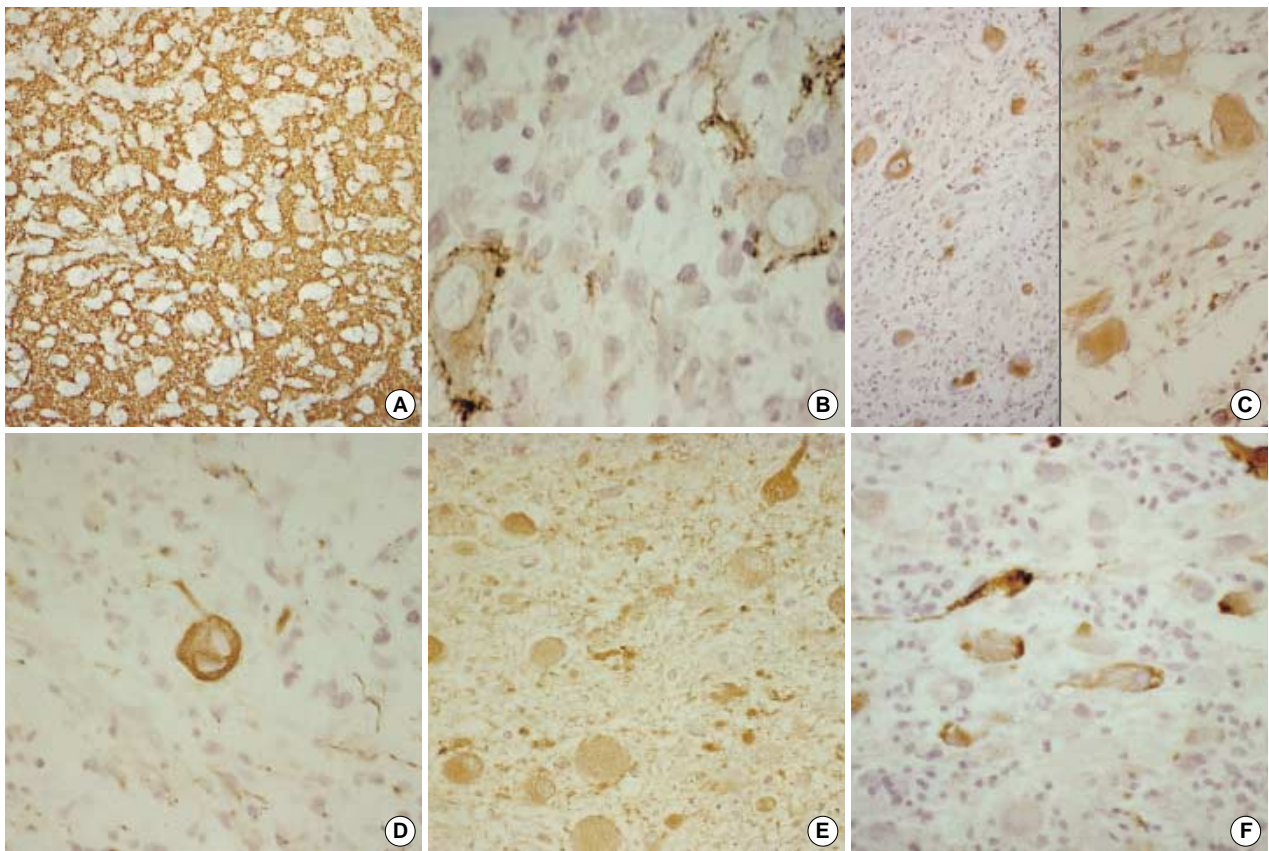


Fig. 2. (A) Normal cortex shows granular immunoreactivity for synaptophysin in the background neuropils with sparing neuronal cells. (B) Perikaryal surface punctate synaptophysin immunoreactivity in neurons of a ganglioglioma. (C) Diffuse perikaryal cytoplasmic synaptophysin immunoreactivity (A-C: synaptophysin immunostain). (D) Immunoreactivity with anti-neurofilament antibody shows axonal positivity (neurofilament immunostain). (E) NSE is expressed in the perikaryal cytoplasm of all neuronal cell component (NSE immunostain). (F) Chromogranin A shows focally but strongly immunoreactive in the perikaryal cytoplasm of neurons (Chromogranin A Immunostain).

neurons (Fig. 2E). Chromogranin A was focally but strongly immunoreactive in the perikaryal cytoplasm of neoplastic neurons in 6 cases and focally and weakly positive in 3 cases (Fig. 2F). The remaining 25 cases showed total negativity for chromogranin A. GFAP revealed immunoreactivity in nonganglionic astrocytic components and their processes. The range of MIB-1 indices showed grade II to be 0.0-1.05% (mean 0.27 ± 0.3), grade III to be 0.7-8.02% (Mean 2.8 ± 3.2), and two cases of grade IV were 3.0 and 4.99%. The nonpaired T-test of the MIB-1 indices had a significant p values (<0.001) between the grade II group and the grade III or IV groups, but there was no significance in the paired T test (p value: 0.13).

DISCUSSION

As in previous reports dealing with ganglion cell tumors, our collected cases have similar clinicopathologic features including age distribution, gender, presentation of symptoms, common tumor sites, and radiological findings described in the result. In our series, the temporal lobe was the most common site (65%), and we found rare cases occurring in the cerebellum and the brainstem. As in other reports, in our series the most common symptom was intractable seizures (73%) in the cases of supratentorial tumors. In the infratentorial tumors, the symptoms secondary to increased intracranial pressure were most common. Neurologic deficits were rarely found in accordance with the tumor site.

The diagnosis of gangliogliomas is occasionally difficult when the neurons are minor components. Wolf *et al.* described that 15% of gangliogliomas contain areas of purely glial cells and emphasized the need for thorough sampling of tumors by surgeons and pathologists.⁹ The neuronal component must be distinguished from the normal residual or entrapped neurons by aberrant location, irregular clustering, abnormal axons, multinucleation or other cytological features of atypia.¹⁰ The presence of neurons must sometimes be clearly identified either by neuronal histochemical or immunohistochemical markers such as synaptophysin, neurofilament and NSE. Binucleate neurons, previously suggested to be common in gangliogliomas, were found in 61.8% (21/34 cases) of our ganglion cell tumors; but the number of binucleate neurons were very rare in individual cases. Miller *et al.*⁴ also reported that binucleate neurons were not common in their series of gangliogliomas. Neurites are often tortuous, misaligned or large.

Until now, malignant transformations of the neuronal cell

were thought to be doubtful. Some authors have suggested that the neuronal cell component may become anaplastic as well as a glial component,^{4,7} because both glial and neuronal cells could proliferate in the tissue culture, and some neurons have atypical features with rare mitoses. Prayson *et al.* emphasized the neoplastic nature of ganglion cells in the ganglion cell tumor, because neurons exhibited prominent immunoreactivity for MIB-1.⁶ Isimbaldi *et al.* also noted three cases in which the dysplastic neurons had atypical and irregular shapes and sizes. However, the possible occurrence of malignant transformation of the neuronal component in ganglion cell tumors remains controversial.¹¹ In our study, we found evidence of malignant transformation in neuronal cells, including bizarre and anaplastic morphology with mitotic activity and MIB-1 immunoreactivity of the neuronal cells in three high grade cases. Our results indicate that both glial and neuronal components can be malignant.

Criteria for the grading of ganglioglioma have not been established. It has been suggested that the clinical prognosis of affected patients depends on the grade of the astrocytic component.¹² Miller *et al.*⁴ and Kleihues *et al.*¹³ stratified their ganglion cell tumor cases according to the presence of cellularity, nuclear atypia, mitotic activity, necrosis, and endothelial proliferation. However, they did not describe precise diagnostic criteria using those parameters. Some pathologists divide tumors into two grades, low grade and high grade, while others use a 3-tiered grading system. The new WHO classification regards the ganglioglioma as a grade 1 tumor, which has a low potential for malignancy and grade 3 malignant counterpart, which eventually may lead to the histological features of glioblastoma.⁵ So we used the Dauma-Duports grading system to easily grade the glial component. In two of the cases, we found real grade IV ganglioglioma with the components of glioblastoma.

Wolf *et al.* reported that the labeling indices for Ki-67 were less than 10% in all but one of the gangliogliomas⁹ and 74% of them showed less than 1% of Ki-67 labelling indices. The mean values of MIB-1 indices ranged from 1.1 to 2.7% in the gangliogliomas.⁵ The study of bromodeoxyuridine uptake in gangliogliomas showed similar results.¹⁴ Thus, Wolf *et al.*⁹ concluded that the percentage of proliferating cells in gangliogliomas is similar to that observed in other low-grade gliomas. In our cases, using the Daumas-Duport/St. Anne Mayo grading system, we found that 24 cases were grade 2, 8 were grade 3, and two were grade 4. The range of MIB-1 indices of grade II gangliogliomas was 0.0-1.05%, that of grade III gangliogliomas was 0.7-8.02% and that of grade IV gangliogliomas was 3.0

and 4.99%, respectively. The nonpaired T-test of the MIB-1 indices had a significant p value (<0.001) between the grade II group and the grade III or grade IV groups, but there was no significance in the paired T test (p value: 0.13).

Some investigators consider that aggressive histological features are not a definite indication of malignancy. Rather, tumor location and resectability are more important determinants of biological behavior.¹⁵ The presence of a tumor in the subarachnoid space, in the cases of the ganglion cell tumor, does not suggest that these tumors are aggressive, like pilocytic astrocytomas.¹⁶

It is unclear whether the perikaryal surface punctate immunoreactive pattern for synaptophysin can discriminate neoplastic neurons from normal neurons, as suggested by Miller *et al.*⁴ In our study, perikaryal surface immunoreactivity was found in neoplastic neurons, but it was not seen in all cases. Moreover, the perikaryal cytoplasm of neurons also strongly positive in some gangliogliomas. Previous ultrastructural studies on ganglion cells demonstrated perikaryal abundant electron dense-core neurosecretory granules,¹⁶⁻¹⁹ which were not found in significant numbers within normal cerebral neurons.¹⁶⁻¹⁹ Since synaptophysin is immunoreactive in the neurosecretory granules, all of the above immunoreactive patterns found in our cases are acceptable. Previous reports²⁰⁻²² indicate synaptophysin-immunostaining patterns in neoplastic neurons are not specific for neoplastic neurons, since those synaptophysin immunostaining patterns are seen in the neurons of normal human spinal cords²¹ or in the normal brain near vascular malformations.²² Quinn emphasized that those patterns clearly are not pathognomonic for glioneuronal tumors and must be interpreted with caution.²² We agree with these opinions, although the neurons in the adjacent normal cortex and dysmorphic neurons did not show these patterns of immunoreactivity for the synaptophysin in our cases. We did not compare synaptophysin immunoreactivity in other diseases or conditions. More studies are necessary to define them.

NSE was expressed in the perikaryal cytoplasm of all neurons, but since the background neurophils were also positive, definite distinguishing the neurons by NSE immunostaining was difficult in some cases. In six of our cases, neuronal chromogranin A immunoreactivity was found. It was also thought to correspond to the abundant dense-core granules demonstrated in neuroectodermal cells on electron microscopy.^{23,24} The expression of chromogranin A in the central nervous system (CNS) is controversial, because usually a monoclonal antibody for chromogranin A fails to react with the CNS neurons.²⁴ For neurofilaments, the axons stained with neurofilaments are

arranged very haphazardly in the ganglion cell tumor, in contrast to those of the normal brain, which are parallel.

What is the pathology of the cortex surrounding ganglion cell tumors, and what is the origin of the seizure focus in patients with ganglion cell tumors? In one series, of the 38 tumors in which there was an adequate amount of tissue adjacent to the resected ganglion cell tumors for evaluation, cortical architectural abnormalities were identified in 50% of them (19/38 cases).⁶ Prayson *et al.*⁶ suggested that gangliogliomas may represent a tumoral form of cortical dysplasia or neoplastic transformation of a dysplastic focus, and resection of the epileptogenic zones adjacent to the tumor may provide added seizure control. Among our 20 cases that had an adequate amount of cortical tissue adjacent to the tumor, we observed a mild degree of cortical dysplasia in 15 of the cases (75%). At the moment, we cannot judge whether this is real preceding or concomitant cortical dysplasia or secondary disorganization by the tumor.

The pathogenesis of ganglion cell tumors is unknown. In view of their association with disorganized cortical architecture (cortical dysplasia), several hypotheses suggest they might be developmental lesions.^{6,25} Wolf *et al.* also suggested that the neuronal component of ganglion cell tumors is malformative rather than neoplastic.⁹ Ganglion cell tumors may arise from glioneuronal hamartomas through a neoplastic transformation of the astrocytic component. Another theory is that the ganglion cell tumor may originate from ectopias of the peripheral autonomic nervous tissue in the central nervous system.^{26,27} A third theory is that ganglion cell tumors may arise from a single stem cell that differentiates into both glial and neuronal cell lines.^{19,28} Further study is needed to understand the pathogenesis of ganglion cell tumors.

What are the important prognostic factors? Prognostic studies from our 34 cases have already been published by Selch *et al.*²⁹ The 4-year actuarial survival of all 34 patients was 75%. Univariate analysis showed that the presence of symptom duration greater than 2 years, seizures, low pathologic tumor grade, and gross total resection were favorable prognostic factors affecting overall survival (Table 2).²⁹ According to multivariate analysis, the two most important favorable prognostic factors impacting overall survival were low tumor grade and gross total resection, although neither achieved statistical significance ($p=0.09$).²⁹ No comment can be made regarding the effects of adjuvant therapy, since only six cases received adjuvant therapy, and they were treated with different types of adjuvant therapy.

In conclusion, the neuronal component also showed malignant transformation with proliferating activity. In our cases, the neo-

Table 2. Univariate and Multivariate analysis on the influence of prognostic factors on overall survival and progression-free survival on 34 patients with gangliogliomas (Quoted from reference 29)

Prognostic variable	Categories	Overall survival (p value)		Progression-free survival (p value)	
		Uni.	Multi.	Uni.	Multi.
Age (years)	<18 yrs/>18 yrs	0.34	-	0.30	-
Gender	M/F	0.16	-	0.33	-
Seizures	Yes/No	0.04	0.28	0.02	0.10
Size	<3 cm/>3 cm	0.32	-	0.39	-
Symptom duration (years)	>2 yrs/<2 yrs	0.02	0.22	0.12	-
Pathologic grade	low/high	0.02	0.09	0.10	-
Surgery	GTR/STR	0.01	0.09	0.02	0.14
Rad-enhancement	Yes/No	0.43	-	0.28	-
Rad-calcifications	Yes/No	0.21	-	0.38	-

GTR: gross total resection, STR: subtotal resection, Uni.: Univariate, Multi: Multivariate, Rad: radiologically, M: male, F: female.

plastic neurons showed different synaptophysin immunoreactive patterns from nonneoplastic neurons, however, it may not be specific for neoplastic neurons. The MIB-1 indices were helpful for grading ganglion cell tumors. Only mild cortical dysplasia was present in the normal cortex adjacent to the tumor; however, it does not explain the pathogenesis of ganglion cell tumors. To eliminate the seizure focus, the excision of the dysplastic cortex, in addition to the tumor, may be required. More experimental study is needed to solve the pathogenesis or to find the epileptogenic area of ganglion cell tumors.

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