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CLINICAL STUDY - PATIENT STUDY

Germinomas in the basal ganglia: magnetic resonance imaging classification and the prognosis

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Abstract Germinoma in the basal ganglia (BG) is notorious for its diagnostic difficulty. Clinical and radiological features of this disease are quite diverse, but have not been well characterized with respect to prognosis. We retrospectively reviewed the clinical course and treatment outcomes of 17 patients with a BG germinoma. The initial magnetic resonance imaging (MRI) features were classified. Clinical features and treatment outcomes were then analyzed with this classification scheme. A Type 1 lesion was defined as a subtle lesion with faint or no contrast enhancement (six patients). Type 2, 3, and 4 lesions were defined as contrast-enhancing lesions and were differentiated by the lesion size and the presence of subependymal seeding (11 patients). Type 1 lesions were distinct from the other lesions. Patients with a Type 1 lesion had a significantly longer time from the initial MRI to diagnosis than patients with Type 2, 3, and 4 lesions ($P = 0.012$). The actuarial progression-free survival and overall survival of patients 5 years after diagnosis were 66 and 77%, respectively. The presence of a Type 1 lesion ($P = 0.004$), a longer time delay in the diagnosis ($P = 0.038$), and radiation therapy without complete ventricular coverage ($P = 0.010$) were significantly associated with tumor progression. Profound motor deficits at diagnosis were associated with deterioration in motor function after tumor remission ($P = 0.035$). Early diagnosis of BG germinomas could affect the ability to control a tumor and neurological outcomes. In particular, high clinical suspicion and active diagnostic procedures are recommended. For optimal treatment, radiation fields should include entire ventricles even if there is no subependymal seeding.

Keywords Germinoma · Basal ganglia · Magnetic resonance imaging · Prognosis · Motor function

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Introduction

Germinoma is the most common intracranial germ cell tumor that develops predominantly in children and adolescents. The development of germinomas in the brain remains enigmatic [1]. Another intriguing aspect of this neoplasm is its location in the brain: the majority of germinomas develop in the midline along the third ventricle, notably in the suprasellar and pineal regions [2]. However, about one-tenth of these neoplasms develop off the midline in the basal ganglia (BG), thalamus, and rarely telencephalon [3–5].

Germinomas arising in the BG present special concerns to clinicians. This disease is notorious for its insidious onset and atypical clinical presentation [6]. Initial

radiological findings are frequently subtle, making it difficult to differentiate the germinomas from nontumorous conditions, such as multiple sclerosis and cerebral infarction [7]. Delay in biopsy and subsequent treatment is not uncommon for germinomas in the BG [4].

Germinomas have an infiltrative growth, destroying surrounding brain parenchymal tissue and causing Wallerian degeneration of white matter tracts [8]. Therefore, atrophy of brain structures such as the cerebrum, basal ganglia, and brainstem have been emphasized as reliable signs of BG germinomas [9, 10]. However, it appears that BG germinomas themselves assume diverse features in magnetic resonance imaging (MRI). For example, some tumors show only subtle abnormality of the BG, which is barely discernible in contrast-enhanced T1-weighted images, whereas others appear as huge masses with intense contrast enhancement [4, 7, 11]. Despite these striking differences in imaging features of BG germinomas, little attention has been paid to the relationship between imaging characteristics, clinical profiles, and treatment outcomes.

The prognosis of germinomas is fair, with long-term overall survival rates exceeding 90% [2, 12]. However, the rate of treatment failure is reported to be higher for BG germinomas than for germinomas in other locations [4]. Moreover, motor weakness in the limbs, which frequently accompanies BG germinomas, can persist even though the disease has been cured [4]. Nonetheless, there are few data regarding the long-term outcomes and prognostic factors for BG germinomas.

In the present study, the long-term treatment outcomes of 17 patients with BG germinomas were analyzed in terms of tumor control and neurological deficits. Specifically, the prognostic implications of radiological features are discussed with respect to the symptomatology, nuclear imaging findings, and treatment outcomes.

Materials and methods

From January 1997 to December 2007, 155 patients were diagnosed with an intracranial germ cell tumor at the Seoul National University Hospital. We included patients with a tumor located in the BG (lentiform nucleus, caudate nucleus, and amygdala) in the study. The patients with a tumor mainly situated in the thalamus and midbrain were excluded from the study. Twenty-one patients (14%) had a tumor involving the BG based on the neuroimaging studies. Eighteen patients were diagnosed with a BG germinoma, and three were diagnosed with a mixed germ cell tumor. One patient with a BG germinoma was lost to follow-up after diagnosis. Therefore, 17 patients with a BG germinoma were included in this study. Fifteen patients were male, and two were female. The median age at diagnosis was 13 years (range, 9–19 years).

Their clinical data of patients were reviewed retrospectively. Information on patients' symptomatology, delay in the biopsy, tumor markers, and treatment protocols were collected. For radiological data, the MRI features of the lesions and characteristic atrophy of corticospinal tracts were analyzed. Positron emission tomography (PET) findings for the tumors were compared with MRI findings.

The median follow-up period was 42 months (range, 13–113 months). The treatment outcomes were evaluated in two tiers: tumor control and neurological sequelae, in particular, changes in preexisting motor weakness. For statistical analyses, SPSS 17.0 (SPSS, Chicago, IL, USA) was used. The Kaplan–Meier method was used to assess progression-free survival (PFS) and overall survival (OS). PFS and OS were calculated from the time of pathological diagnosis. For revealing relevant prognostic factors, a log rank test was used for dichotomous variables in the univariate analysis. A Cox proportional hazards model was used for continuous variables. Because of the small number of cases and its low statistical power, multivariate analysis was not applied. The significance level was 5%.

Results

MRI features and classification

All patients had at least one brain MRI examination before the pathological diagnosis, although the sequences and protocols of MRI varied. The lesion mainly involved the lentiform nucleus in all patients. Other structures involved included the caudate nucleus, the internal capsule, the thalamus, and rarely the amygdaloid complex. The BG lesions in the initial MRI were categorized into four distinct patterns: Type 1, a subtle patchy lesion visible mainly in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with faint or no contrast enhancement (six patients); Type 2, a small lesion (<3 cm in diameter) with nodular contrast enhancement (three patients); Type 3, a small BG lesion with subependymal seeding that showed intense contrast enhancement (two patients); and Type 4, a large lesion (≥3 cm in diameter) that showed intense contrast enhancement and mass effect (six patients) (Fig. 1).

Four patients had multiple lesions involving the bilateral BG. Spinal MRI was performed on 15 patients, and cerebrospinal fluid (CSF) cytology was obtained from 14 patients before the biopsy. No CSF dissemination was found in these examinations.

When the initial MRI was reviewed retrospectively, atrophy of the cerebral peduncle was evident in 15 patients

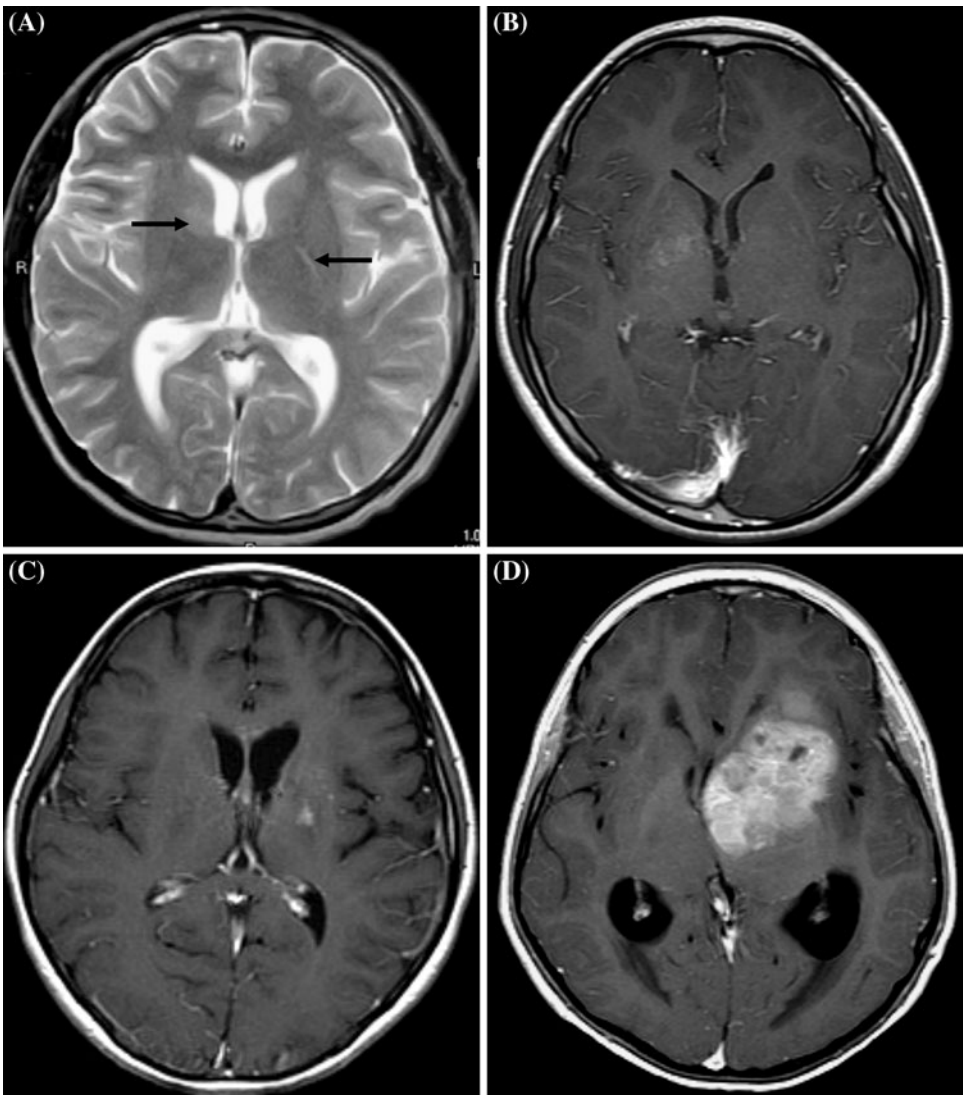

Fig. 1 Magnetic resonance imaging classification of basal ganglia (BG) germinomas. Type 1: a subtle patchy lesion visible mainly in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with faint or no contrast enhancement (six patients); Type 2: a small lesion (<3 cm in diameter) with nodular contrast enhancement (three patients); Type 3: a BG lesion with subependymal seeding that shows intense contrast enhancement (two patients). Type 4: a large lesion (≥3 cm in diameter) that shows intense contrast enhancement and mass effect (six patients). **a** A Type 1 lesion showing subtle patchy high signal intensity in the right BG (*arrow*) in a T2-weighted image. There is also a suspicious lesion in the left internal capsule (*arrow*). No enhancement was observed in T1-weighted images (not shown). **b** A Type 2 lesion with a small lesion in the right BG shows a nodular enhancement pattern. **c** A Type 3 lesion in the left BG accompanied by subependymal seeding. **d** A Type 4 lesion showing a huge mass in the left BG with intense contrast enhancement and mass effect

(88%). BG atrophy, especially in the head of the caudate nucleus, was observed in 14 patients (82%). Hemispheric (cerebral cortical) atrophy was found in one patient (6%). The patient with hemispheric atrophy had a Type 2 BG lesion on the initial MRI (Fig. 2).

Symptomatology

Hemiparesis was the most common initial complaint, and was found in 10 patients (59%). Two patients presented with dystonia in the distal extremities. Abnormal behaviors such as bizarre or aggressive behavior were the chief complaints in two patients. Symptoms related to increased intracranial pressure (ICP), such as headache and projectile vomiting, were found in one patient. Intriguingly, one patient initially presented with unexplainable hiccups and vomiting that was not related to increased ICP.

At the time of diagnosis, hemiparesis was evident in all patients. Seven patients had a profound motor deficit of grade 3 or less and/or a joint contracture. Bulbar signs such as hoarseness and dysphagia were observed in seven patients (41%). Abnormal behaviors and symptoms related to increased ICP were found in four (24%) and three patients (18%), respectively. Hiccups and vomiting not related to increased ICP were found in two patients (12%) at the time of diagnosis.

The symptomatology was related to the MRI types. Two-thirds of the patients with a Type 1 lesion had profound motor deficits at the time of diagnosis. Hiccups and vomiting without other signs of increased ICP developed exclusively in patients with a Type 1 lesion. These two patients had bilateral lesions. Headache and vomiting related to increased ICP were the presenting symptoms of a patient with a Type 4 BG lesion. The MRI types and symptomatology of patients are summarized in Table 1.

The patients sought medical attention after a median period of 2 months (range, 3 days to 10 months) from symptom onset. The median time from the first visit to a

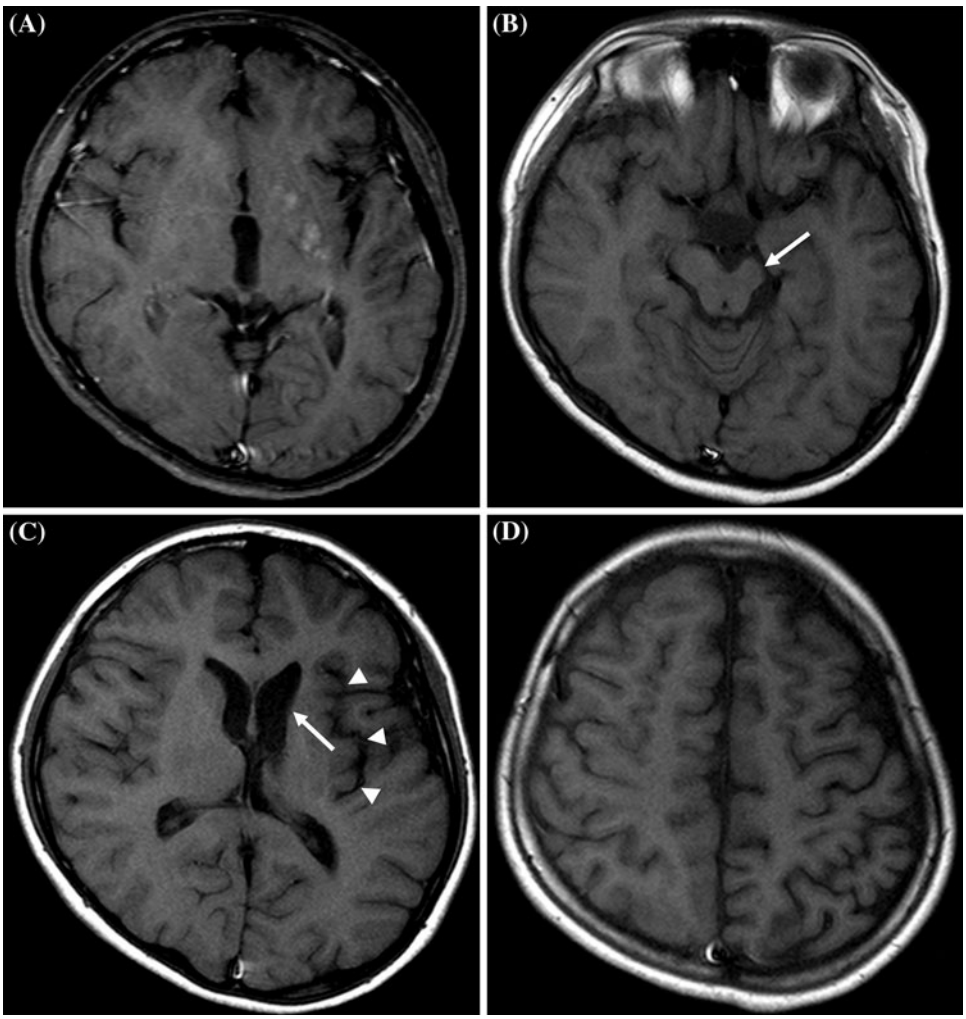

Fig. 2 Characteristic atrophic signs of a basal ganglia (BG) germinoma. T1-weighted magnetic resonance images from a patient with a Type 2 lesion in the left BG. **a** A nodular enhancing tumor is observed in the left BG. **b** Atrophy of the left cerebral peduncle (*arrow*). **c** Atrophy of the left BG, indicated by the caudate nucleus head (*arrow*). The widening of the left Sylvian fissure (*arrowheads*) also reflects atrophy of the left BG. **d** Diffuse widening of the sulci in the left cerebral hemisphere (*arrowheads*) shows cortical atrophy

medical doctor to initial MRI examination was 0.5 months (range, 0.2–9 months). The median time from the initial MRI examination to surgical biopsy was also 0.5 months (range, 0.1–30 months). However, patients with a Type 1 lesion had a significantly longer time to biopsy (median 11 months; range, 2–30 months) compared with other patients ($P = 0.012$; Kruskal–Wallis test; Fig. 3). During the diagnostic delay, patients with a Type 1 BG lesion received multiple MRI examinations. The MRI taken at the time of surgical biopsy revealed tumor progression in all patients: contrast-enhancing tumors (8–35 mm in diameter) developed in all patients, and subependymal seeding occurred in two patients.

During the diagnostic delay, 11 patients were misdiagnosed with other nontumorous diseases. Four of these patients had multiple diagnoses: stroke (four patients), multiple sclerosis (three patients), various musculoskeletal problems (two patients), Wilson's disease (two patients), depression (two patients), moyamoya disease (one patient), gastroesophageal reflux (one patient), and psychogenic vomiting (one patient). The patients with a Type 1 lesion were more frequently misdiagnosed than were patients with other types of lesions, reflecting their longer diagnostic delay ($P = 0.043$; Fisher's exact test).

Positron emission tomography (PET)

^{18}F-fluorodeoxyglucose (FDG)-PET of the brain was obtained in seven patients for initial diagnosis (Fig. 4). In all patients, ^{18}F-FDG-PET showed relative hypometabolism in the BG lesions regardless of the MRI type, compared with mild FDG uptake in the contralateral BG and surrounding structures. Hypometabolism of ^{18}F-FDG-PET was not confined to the BG lesions, and was also found in the ipsilateral cerebral hemisphere in all patients. Hypometabolism in the contralateral cerebellar hemisphere because of diaschisis was noted in all patients. Two patients underwent ^{18}F-FDG-PET for the diagnosis of recurrence, and the results revealed mild hypometabolism in the lesion sites.

^{11}C-methionine-PET was conducted in three patients for the diagnosis of recurrence (Fig. 5). Recurrent germinomas

Table 1 Symptoms and signs of the patients at initial presentation and at the time of diagnosis

Case no.	Sex	Age at diagnosis	Initial MRI type	Multiplicity	Delay in diagnosis (month)[a]	Symptoms at initial presentation	Symptoms at diagnosis
1	M	13	1	Bilateral BG	30	Hemiparesis	Hemiparesis,[b] bulbar sign, abnormal behavior, hiccup/vomiting (non-IICP-related)
2	M	9	1	–	9	Hemiparesis	Hemiparesis,[b] bulblar sign, memory disturbance
3	M	17	1	–	16	Hemiparesis	Hemiparesis,[b] headache/vomiting
4	M	15	1	Bilateral BG	13	Hiccup/vomiting (non-IICP-related)	Hemiparesis, hiccup/vomiting (non-IICP-related)
5	M	9	1	–	2	Dystonia	Hemiparesis,[b] dystonia
6	M	19	1	Bilateral BG	8	Hemiparesis	Hemiparesis, bulbar sign
7	M	12	2	–	0.5	Hemiparesis	Hemiparesis, headache/vomiting
8	M	14	2	–	0.3	Hemiparesis	Hemiparesis, bulbar sign, polyuria/polydipsia, growth retardation
9	M	13	2	–	0.5	Hemiparesis	Hemiparesis
10	F	13	3	Bilateral BG, subependymal seeding	3	Chorea, abnormal behavior, memory disturbance, poor school performance	Hemiparesis,[b] bulbar sign, chorea, dystonia, abnormal behavior, memory disturbance, poor school performance
11	M	13	3	Septum, frontal horn	0.3	Polyuria/polydipsia	Hemiparesis, polyuria/polydipsia, growth retardation, memory disturbance, poor school performance
12	M	11	4	–	3	Dystonia	Hemiparesis, bulbar sign, dystonia, polyuria/polydipsia, abnormal behavior
13	M	11	4	–	0.3	Hemiparesis	Hemiparesis
14	F	15	4	–	0.3	Hemiparesis	Hemiparesis[b]
15	M	14	4	–	0.3	Abnormal behavior, poor school performance	Hemiparesis, bulbar sign, abnormal behavior, poor school performance
16	M	9	4	–	0.1	Headache/vomiting	Hemiparesis,[b] headache/vomiting
17	M	14	4	–	0.2	Hemiparesis	Hemiparesis, hemisensory loss, visual disturbance

M male, *F* female, *MRI* magnetic resonance image, *BG* basal ganglia, *IICP* increased intracranial pressure

[a] Delay in diagnosis means the time interval from the initial MRI to the surgical biopsy (definite diagnosis)

[b] Profound motor weakness of grade ≤ 3 and/or accompanied by a joint contracture

were observed as hypermetabolic lesions on ^{11}C-methionine-PET in the three patients.

Tumor markers and biopsies

The levels of serum tumor markers, alpha-fetoprotein (αFP) and beta-human chorionic gonadotrophin (β-hCG) were measured in all patients. Tumor marker levels in the CSF were checked in 12 patients. However, the time of tumor marker measurement was quite variable, especially for the CSF values. Elevation of serum and CSF β-hCG was detected in three patients (11–99 mIU/ml) and five patients (12–142 mIU/ml), respectively. No elevation of αFP was noted in any patient.

Sixteen patients received a stereotactic biopsy, and one patient received an open biopsy. Pathological examination revealed a germinoma in all patients.

Treatment

All patients with a germinoma received up-front chemotherapy. In the 1990s, cisplatin-based regimens such as the Children's Cancer Group (CCG)-9921 or -9931 protocols were applied (three patients). From the early 2000 to 2004, the BEP regimen consisting of bleomycin, etoposide, and cisplatin was used (six patients). From 2005 to the present, the Korean Society for Pediatric Neuro-Oncology (KSPNO)-G051 protocol has been used (eight patients). The KSPNO-G051 protocol consists of four cycles of carboplatin and etoposide alternating with cyclophosphamide and etoposide.

All patients with a germinoma received radiation therapy (RT) after the up-front chemotherapy. For the four patients with subependymal seeding at diagnosis (M^+ group; two patients with a Type 3 lesion and two patients

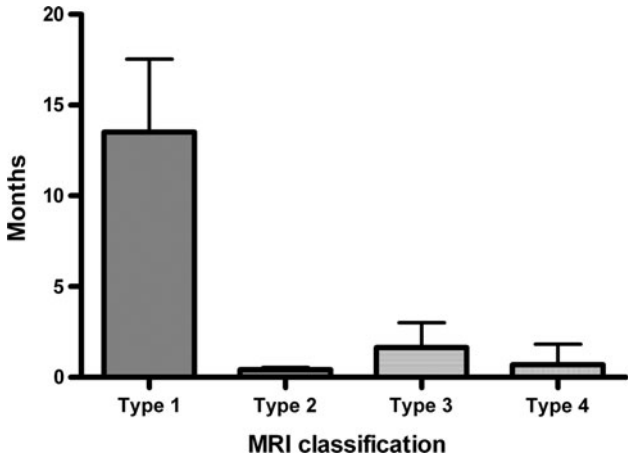

Fig. 3 Delay in the biopsy according to the magnetic resonance imaging (MRI) classification. Delay in the biopsy was defined as the time between the initial MRI examination and surgical biopsy. Patients with a Type 1 lesion had a significantly longer delay than other patients ($P = 0.012$; Kruskal–Wallis test). Error bars indicate standard error of the mean

with a initial Type 1 lesion), the radiation field included the BG lesion and the entire ventricular system (to the whole ventricles in two patients; to the craniospinal axis in two patients). For the 13 patients without subependymal seeding (M^- group), the radiation field was limited to the BG lesion in four patients (39.6–54 Gy), but was extended to the entire ventricles in nine patients (to the entire ventricles in five patients; to the whole brain in one patient; to the craniospinal axis in three patients).

Tumor control and survival

The patient's clinical profiles, treatment protocols, and oncological outcomes are summarized in Table 2. After up-front chemotherapy and radiation therapy, complete remission was achieved in all patients. After a median follow-up period of 42 months (range, 13–113 months) from the pathological diagnosis, tumor progression occurred in four patients, and this was fatal in three patients.

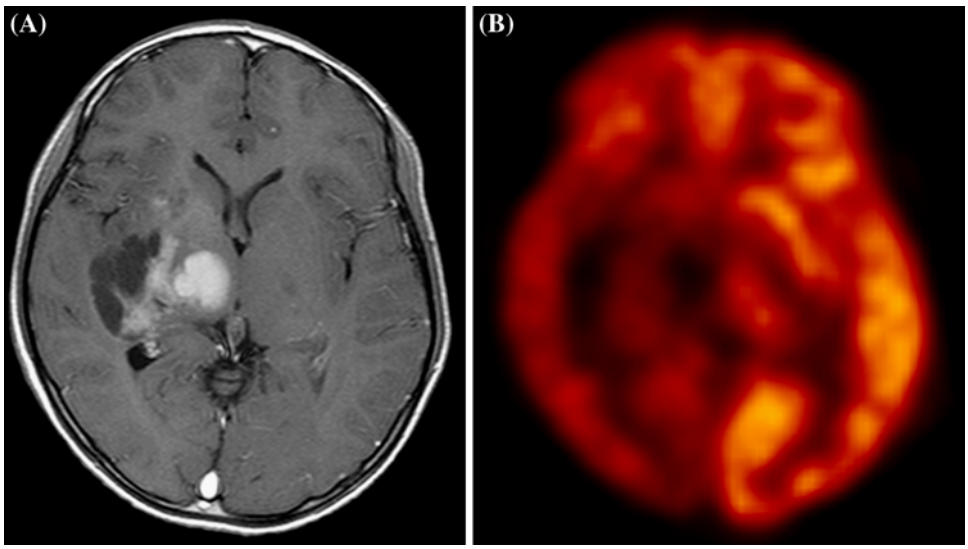

Fig. 4 A huge germinoma in the left basal ganglia (a Type 4 lesion) was relatively hypometabolic on ^{18}F-fluorodeoxyglucose-PET

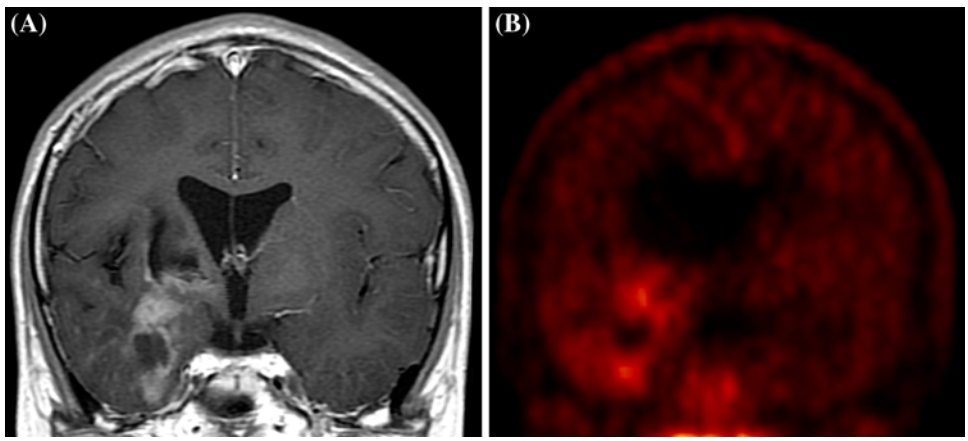

Fig. 5 A 9-year-old boy (Case 5) with a germinoma in the right basal ganglia (BG) received up-front chemotherapy and radiation therapy (39.6 Gy to the right BG). He underwent complete remission of the tumor. Three years later, multifocal enhancing lesions developed in the right ventral BG and temporal lobe on follow-up magnetic resonance imaging. ^{11}C-Methionine-PET demonstrated hypermetabolic lesions in the same regions

Table 2 Clinical profiles, treatment protocols, and outcome of the patients

Case no.	Initial MRI type	FDG-PET	Methonine-PET	Seeding at diagnosis	β-hCG	Chemotherapy	Radiation (Gy)	Profound motor deficit[d]	Motor function	Progress	PFS (month)	Survival	OS (month)
1	1	Hypo[a]	NA	Yes	Elevated[b, c]	9931	BG lesion 54; WV 54	Yes	Deteriorated	Yes	35	Expired	48
2	1	Hypo	Hyper[a]	No	Elevated[b]	KSPNO	BG lesion 39.6	Yes	No change	Yes	13	Expired	25
3	1	Hypo[a]	Hyper[a]	No	Normal	BEP	BG lesion 54	Yes	Deteriorated	Yes	30	Expired	86
4	1	NA	NA	Yes	Elevated[b]	KSPNO	BG lesion 27; CSA 23.4	No	No change	No	43	Alive	43
5	1	NA	Hyper[a]	No	Elevated[b]	KSPNO	BG lesion 39.6	Yes	No change	Yes	38	Alive	45
6	1	NA	NA	No	Normal	BEP	BG lesion 50.4; WV 36	No	No change	No	13	Alive	13
7	2	NA	NA	No	Normal	KSPNO	BG lesion 30.6; WV 23.4	No	Improved	No	18	Alive	18
8	2	Hypo	NA	No	Normal	KSPNO	BG lesion 45; WV 23.4	No	Improved	No	54	Alive	54
9	2	Hypo	NA	No	Elevated[b, c]	KSPNO	BG lesion 45; CSA 25.2	No	No change	No	14	Alive	14
10	3	NA	NA	Yes	Normal	BEP	BG lesion 54; WB 36; WS 21	Yes	Deteriorated	No	42	Alive	42
11	3	NA	NA	Yes	Normal	9921	BG lesion 50.4; WV 50.4	No	No change	No	113	Alive	113
12	4	NA	NA	No	Normal	BEP	BG lesion 45; WV 45	No	Deteriorated	No	48	Alive	48
13	4	Hypo	NA	No	Normal	KSPNO	BG lesion 50.4; WB 23.4	No	No change	No	30	Alive	30
14	4	Hypo	NA	No	Normal	BEP	BG lesion 50.4; CSA 23.4	Yes	Deteriorated	No	36	Alive	36
15	4	NA	NA	No	Normal	BEP	BG lesion 54	No	No change	No	34	Alive	34
16	4	Hypo	NA	No	Elevated[b, c]	9931	BG lesion 54; CSA 23.4	Yes	Deteriorated	No	80	Alive	80
17	4	Hypo	NA	No	Normal	KSPNO	BG lesion 25.2; WV 19.8	No	Improved	No	22	Alive	22

MRI magnetic resonance image, *FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *Methionine-PET* ^{11}C-methionine PET, *NA* not assessed, *Hypo* hypometabolism, *Hyper* hypermetabloism, *hCG* human chorionic gonadotrophin, *9931* Children's Cancer Group 9931 protocol, *KSPNO* Korean Society for Pediatric Neurooncology Protocol for Germinomas, *BEP* bleomycin/etoposide/cisplatin, *9921* Children's Cancer Group 9921 protocol, *BG* basal ganglia, *WV* whole ventricle, *CSA* craniospinal axis, *WB* whole brain, *WS* whole spine, *PFS* progression-free survival, *OS* overall survival

[a] The PET scan was taken for the diagnosis of a recurred tumor

[b] The β-hCG was elevated in the cerebrospinal fluid

[c] The β-hCG was elevated in serum

[d] Motor weakness of grade ≤3 and/or accompanied by a joint contracture

Two patients had tumor recurrence in the temporal lobe and fronto-temporal lobe, respectively. Two patients had recurrence with diffuse subependymal and leptomeningeal seeding. The actuarial PFS rates in the second and the fifth years of follow-up were 86 and 66%, respectively. The actuarial OS rates in the second and the fifth years were 100 and 77%, respectively.

In the univariate analysis using a Kaplan–Meier model for dichotomous variables, the patients with a Type 1 lesion had a significantly higher risk of tumor progression than the patient with a lesion of other MRI types ($P = 0.004$; log rank test; Fig. 6). The strategy in the RT also affected tumor control. In the M^+ group (four patients) in whom the radiation field included the whole ventricles, one patient experienced tumor progression by local failure. In the M^- group (13 patients), four patients received radiation limited to the BG lesion and nine patients received RT including the whole ventricles. Tumor progression occurred exclusively in the former patients: three patients who received limited RT had tumor progression. Furthermore, all three patients had tumor recurrence outside the BG. Statistically, RT limited to the BG tumor was significantly related to tumor progression in the M^- group ($P = 0.010$; log rank test). Subependymal seeding or elevated β-hCG in serum and/or CSF before the treatment were not significant variables ($P = 0.640$ and $P = 0.138$, respectively; log rank test).

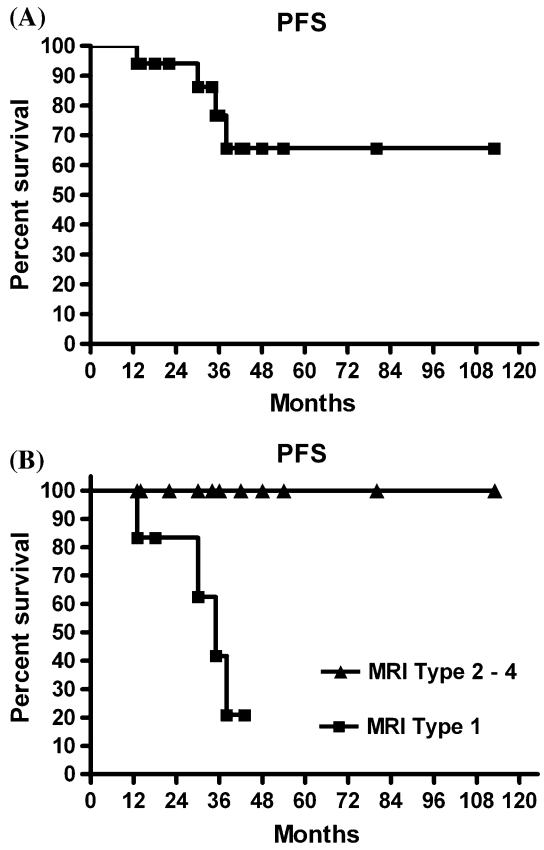

Fig. 6 Survival functions for progression-free survival (PFS) of the 17 patients. **a** The actuarial progression-free survival (PFS) rates at the second and the fifth years of follow-up were 86 and 66%, respectively. **b** Patients with a Type 1 lesion showed a shorter PFS than patients with other MRI types (Types 2–4) ($P = 0.004$; log rank test)

Univariate analyses using a Cox proportional hazards model for continuous variables demonstrated that a longer delay in the diagnosis was significantly associated with tumor control failure ($P = 0.038$, relative risk = 1.098/month; Cox regression). Age at diagnosis was not a significant variable ($P = 0.629$, relative risk = 0.902/year; Cox regression).

Neurological outcomes

Three patients experienced an improvement in preexisting hemiparesis. These three patients had motor weakness of muscle power grade 4 and no contracture at diagnosis. Eight patients had no remarkable change in their hemiparesis after the treatment. Six patients experienced worsened hemiparesis, although complete remission of the tumor was achieved. Five of these patients had a profound motor deficit of muscle power grade 3 or less and/or a joint contracture. The presence of a profound motor deficit at diagnosis was significantly correlated with motor deterioration after complete remission of the tumor ($P = 0.035$; Fisher's exact test).

Abnormal behaviors (bizarre, depressive, or psychotic behaviors) improved in only one patient after the treatment. Three of the four patients with behavioral problems at diagnosis remained unchanged or worsened. Furthermore, one patient without preexisting behavior problems developed an impulsive and aggressive behavioral characteristic despite complete remission of the tumor.

Discussion

Germinomas in the BG region are known for their peculiar symptomatology, ambiguous neuroradiological findings, and difficulty in diagnosis. To date, few studies on the long-term clinical outcomes of patients with germinomas in the BG region have been reported, mainly because of the low incidence of this disease. Sonoda et al. [4] reported on the long-term clinical outcomes of 10 patients with a BG germinoma recruited over two decades. In this study, we included 17 patients with a BG germinoma who were diagnosed over a relatively short time (one decade).

Furthermore, the diverse MRI features of BG germinomas, ranging from subtle nonenhancing patchy lesions to huge enhancing masses, have not been analyzed with respect to symptomatology and prognosis. A literature

review shows that several distinct neuroimaging patterns of BG germinomas have been reported, including subtle patchy lesions in the BG with or without contrast enhancement, and a large enhancing mass exerting a mass effect on surrounding structures [4, 11, 13, 14]. Multifocal germinomas involving the BG and other foci have also been recognized [4, 15]. We observed all these initial MRI patterns in our patients and classified them into four categories. Type 1 lesions are distinct from the rest of the MRI types because they showed faint or no contrast enhancement and are easily mistaken for a nontumorous condition. Therefore, delay in taking a biopsy, which was defined as the time from the initial MRI examination to the surgical biopsy, was significantly longer for patients with Type 1 lesions than for patients with lesions of other MRI types. The symptomatology of the patients with a Type 1 lesion was also distinct. Although progressive hemiparesis was the most common symptom in this group, like the other groups, hemiparesis more frequently progressed into profound motor deficits during the longer diagnostic delay in this group. This profound motor deficit, defined as motor grade 3 or less and/or a joint contracture, correlated with motor function deterioration after treatment.

Hiccups and vomiting not related to an increased ICP were found only in this group (two patients). One patient developed symptoms before the emergence of hemiparesis, and the other developed symptoms after the recognition of progressive hemiparesis. Gastroesophageal reflux, psychogenic vomiting, and multiple sclerosis were also suspected in these patients. The pathophysiology of the hiccups and vomiting is obscure, because pathological hiccups and vomiting are signs of a brainstem lesion [16]. The fact that these two patients had bilateral BG lesions may be related to the development of these atypical symptoms. It is also possible that these symptoms were caused by occult seeding in the medulla oblongata because these patients developed subependymal seeding of tumor at the time of pathological diagnosis.

Based on our data, Type 1 lesions progressed into overt tumors with radiological features that looked like Type 2, 3, and 4 lesions over a rather long symptomatic period. In contrast, patients with Type 2, 3, and 4 lesions on the initial MRI had a very short symptomatic period before the MRI examination in this study. Therefore, germinomas of Type 1 classification may be biologically different lesions from germinomas of the other three classification types. An insidious clinical course with apparently normal neuroimaging findings is characteristic of some germinomas [17]. In suprasellar germinomas, a long-term clinical latency period after the onset of diabetes insipidus is frequently seen before a contrast-enhancing mass was visible with MRI [18].

Because of the ambiguity in neuroimaging features, metabolic imaging using PET is a promising diagnostic tool for BG germinomas. In this study, ^{18}F-FDG-PET showed a specific pattern for the primary BG germinomas. Virtually all BG germinomas, whether a subtle lesion (Type 1) or a huge mass (Type 4), showed hypometabolism. Therefore, it may be difficult to differentiate Type 1 BG germinomas from benign pathological lesions, such as a cerebral infarction, using ^{18}F-FDG-PET. However, ^{18}F-FDG-PET can be useful in distinguishing germinomas from other brain tumors arising in the BG, such as high-grade glioma, primitive neuroectodermal tumor, and lymphoma.

In the literature, several studies report that ^{11}C-methionine-PET demonstrates high sensitivity for detecting BG germinomas [7, 19, 20]. In our study, ^{11}C-methionine-PET also showed a high diagnostic value for recurrent germinomas. Therefore, high clinical suspicion and active diagnostic procedures aided by ^{11}C-methionine-PET are required to diagnose subtle Type 1 lesions.

In this study, the 5-year actuarial PFS and OS rates were 66 and 77%, respectively. These figures are lower than the values reported for germinomas in general [12, 21]. Sonoda et al. [4] reported three cases of recurrence and one death in 10 patient with BG germinomas. It is uncertain whether BG germinomas have a worse prognosis than germinomas in other locations. Nonetheless, our results revealed some relevant points regarding this issue. First, a longer diagnostic delay has a bad influence on treatment outcomes for patients with BG germinomas. During the period of diagnostic delay, the occult lesions developed into a full-blown disease. Second, four patients without subependymal seeding received RT limited to the BG lesion without complete ventricular coverage, and three of these patients experienced tumor recurrence. Involved field radiation without complete ventricular coverage resulted in less-favorable outcomes in other studies [22, 23].

The improvement of motor weakness in patients with a BG germinoma is a controversial issue. There are case reports that document improved hemiparesis in patients with a BG germinoma after successful treatment [24]. However, a recent clinical series on BG germ cell tumors negates the possibility of improvement in motor function even when the disease has been cured [4]. Our results showed that recovery of motor function is possible in a small portion of the patients (three out of 17 patients). The outcome of motor function was significantly influenced by the degree of deficit before the treatment, and there is a higher chance of these problems worsening if a profound motor deficit exists. This finding indicates that early diagnosis is important for the preservation of motor function.

Conclusion

Subtle BG germinomas that show faint or no contrast enhancement are easily mistaken for other benign conditions, which delays definitive diagnosis and treatment. Early diagnosis of BG germinomas could affect PFS and neurological outcomes. In particular, high clinical suspicion and active diagnostic procedures are recommended for patients with a subtle BG lesion and an insidious symptomatic onset. For optimal treatment, the radiation field should include the entire ventricular system even if there is no subependymal seeding.

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References

1. Sano K (1999) Pathogenesis of intracranial germ cell tumors reconsidered. J Neurosurg 90:258–264
2. Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N et al (1997) Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 86:446–455
3. Utsuki S, Oka H, Tanizaki Y, Kondo K, Fujii K (2005) Radiological features of germinoma arising from atypical locations. Neurol Med Chir (Tokyo) 45:268–271
4. Sonoda Y, Kumabe T, Sugiyama S, Kanamori M, Yamashita Y, Saito R et al (2008) Germ cell tumors in the basal ganglia: problems of early diagnosis and treatment. J Neurosurg Pediatr 2:118–124
5. Tamaki N, Lin T, Shirataki K, Hosoda K, Kurata H, Matsumoto S et al (1990) Germ cell tumors of the thalamus and the basal ganglia. Childs Nerv Syst 6:3–7
6. Takeda N, Fujita K, Katayama S, Uchihashi Y, Okamura Y, Nigami H et al (2004) Germinoma of the basal ganglia. An 8-year asymptomatic history after detection of abnormality on CT. Pediatr Neurosurg 40:306–311
7. Kawai N, Miyake K, Nishiyama Y, Yamamoto Y, Miki A, Haba R et al (2008) Targeting optimal biopsy location in basal ganglia germinoma using (11)C-methionine positron emission tomography. Surg Neurol 70:408–413
8. Wang KC, Kim SK, Park SH, Kim IO, Cho BK (2006) Intracranial germ cell tumors. In: Tonn JC, Westphal M, Rutka JT et al (eds) Neuro-oncology of CNS tumors. Springer, Berlin, pp 517–527
9. Kim CH, Paek SH, Park IA, Chi JG, Kim DG (2002) Cerebral germinoma with hemiatrophy of the brain: report of three cases. Acta Neurochir (Wien) 144:145–150
10. Nagata K, Nikaido Y, Yuasa T, Fujimoto K, Kim YJ, Inoue M (1998) Germinoma causing wallerian degeneration. Case report and review of the literature. J Neurosurg 88:126–128
11. Moon WK, Chang KH, Kim IO, Han MH, Choi CG, Suh DC et al (1994) Germinomas of the basal ganglia and thalamus: MR findings and a comparison between MR and CT. AJR Am J Roentgenol 162:1413–1417
12. Osuka S, Tsuboi K, Takano S, Ishikawa E, Matsushita A, Tokuuye K et al (2007) Long-term outcome of patients with intracranial germinoma. J Neurooncol 83:71–79
13. Okamoto K, Ito J, Ishikawa K, Morii K, Yamada M, Takahashi N et al (2002) Atrophy of the basal ganglia as the initial diagnostic sign of germinoma in the basal ganglia. Neuroradiology 44: 389–394
14. Ozelame RV, Shroff M, Wood B, Bouffet E, Bartels U, Drake JM et al (2006) Basal ganglia germinoma in children with associated ipsilateral cerebral and brain stem hemiatrophy. Pediatr Radiol 36:325–330
15. Tang J, Ma Z, Luo S, Zhang Y, Jia G, Zhang J (2008) The germinomas arising from the basal ganglia and thalamus. Childs Nerv Syst 24:303–306
16. Musumeci A, Cristofori L, Bricolo A (2000) Persistent hiccup as presenting symptom in medulla oblongata cavernoma: a case report and review of the literature. Clin Neurol Neurosurg 102:13–17
17. Birnbaum T, Pellkofer H, Buettner U (2008) Intracranial germinoma clinically mimicking chronic progressive multiple sclerosis. J Neurol 255:775–776
18. Ramelli GP, Von der Weid N, Stanga Z, Mullis PE, Buergi U (1998) Suprasellar germinomas in childhood and adolescence: diagnostic pitfalls. J Pediatr Endocrinol Metab 11:693–697
19. Lee J, Lee BL, Yoo KH, Sung KW, Koo HH, Lee SJ et al (2009) Atypical basal ganglia germinoma presenting as cerebral hemiatrophy: diagnosis and follow-up with (11)C-methionine positron emission tomography. Childs Nerv Syst 25:29–37
20. Sudo A, Shiga T, Okajima M, Takano K, Terae S, Sawamura Y et al (2003) High uptake on 11C-methionine positron emission tomographic scan of basal ganglia germinoma with cerebral hemiatrophy. AJNR Am J Neuroradiol 24:1909–1911
21. Kawabata Y, Takahashi JA, Arakawa Y, Shirahata M, Hashimoto N (2008) Long term outcomes in patients with intracranial germinomas: a single institution experience of irradiation with or without chemotherapy. J Neurooncol 88:161–167
22. Haddock MG, Schild SE, Scheithauer BW, Schomberg PJ (1997) Radiation therapy for histologically confirmed primary central nervous system germinoma. Int J Radiat Oncol Biol Phys 38: 915–923
23. Nakamura H, Takeshima H, Makino K, Kochi M, Ushio Y, Kuratsu J (2006) Recurrent intracranial germinoma outside the initial radiation field: a single-institution study. Acta Oncol 45:476–483
24. Tsuchida Y, Tsuboi K, Yanaka K, Nose T (1993) Basal ganglia germinoma with crossed cerebellar diaschisis—case report. Neurol Med Chir (Tokyo) 33:779–782