

Diagnostic Imaging of Intracranial Germ Cell Tumors: A Review

Takamitsu Fujimaki
 Department of Neurosurgery,
 Saitama Medical University, Moroyama,
 Japan

1. Introduction

Intracranial germ cell tumors (CNS GCTs) are malignant neoplasms affecting mostly children and young adults. About 95% of affected patients are less than 24 years of age (Figure 1) [1], and males are affected more often than females, approximately three-quarters to four-fifths of patients being male [1, 2].

Number of patients

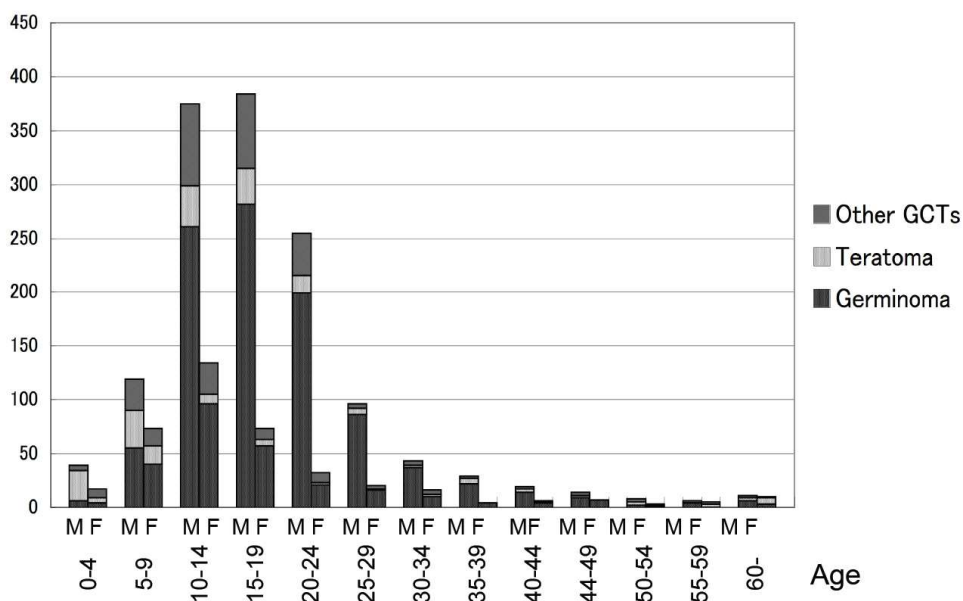


Fig. 1. Age and sex distribution of germ cell tumors (The Brain Tumor Registry of Japan (1)).

CNS GCTs are histologically classified into several histological subtypes, i.e. germinoma, teratoma (mature teratoma, immature teratoma, teratoma with malignant transformation), embryonal carcinoma, yolk sac tumor and choriocarcinoma [3, 4], and some are composed of a mixture of these subtypes. Germinomas are the most frequent histological subtype, followed in order by teratomas, choriocarcinomas, embryonal carcinomas and yolk sac tumors. Mixtures of these tumors are also common, and in fact one third of intracranial germ cell tumors are of mixed types. Among these, germinomas show typical histological patterns, being similar to dysgerminoma of the ovary or seminoma of the testis. They are composed of large round cells and small lymphocytes, thus their histological feature is known as the “two cell pattern”.

The most frequently affected site is the pineal gland, followed by the neurohypophyseal (or “suprasellar”) region (Figure 2). However, these tumors can also arise in the basal ganglia or any other intracranial location.

Number of patients

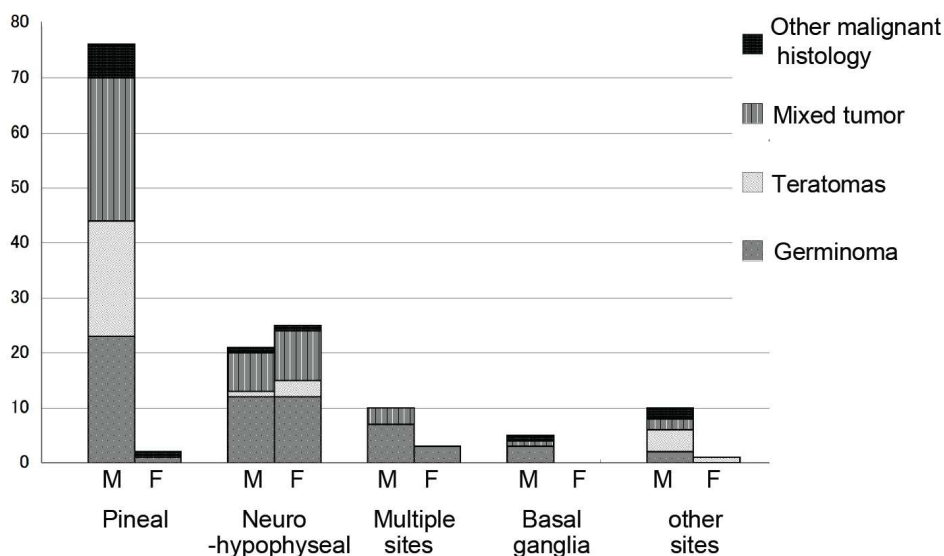


Fig. 2. Location and distribution of histological subtypes (according to Matsutani et al. (2)).

Although, biologically, all intracranial germ cell tumors, except for mature teratomas, are malignant, their clinical characteristics differ. Germinomas respond well to chemo-radiotherapy and their prognosis is relatively good. Mixed tumors composed of any type of teratoma and germinoma are also responsive to appropriate forms of combined therapy including surgery, radiation and/or chemotherapy, and thus their prognosis is better than that of other histological subtypes such as embryonal carcinoma, yolk sac tumor, choriocarcinoma or their mixtures (the so-called “poor prognosis” group), which require more intensive forms of chemo-radiotherapy [5, 6]. For this reason, accurate differential diagnosis of these histological subtypes is very important in a clinical setting.

2. Modalities important for diagnosis of CNS GCTs

Although pathological diagnosis by biopsy is essential for the planning of appropriate treatment for CNS GCTs, tentative histological diagnosis also plays a significant role in deciding the optimal surgical strategy. In this connection, both neuroimaging and assessment of tumor markers are important. Some CNS GCTs produce tumor markers that are helpful for indicating the histological subtype (Table 1). Typically, choriocarcinoma produces the beta-subunit of human chorionic gonadotropin (β -hCG) whereas yolk sac tumor produces alpha-fetoprotein (α -FP). If the serum level of β -hCG alone is elevated to more than 500 mIU/ml, or if that of α -FP alone is elevated to more than 500 ng/mL, then pure choriocarcinoma or yolk sac tumor is considered highly likely, respectively. The levels of markers associated with mixed germ cell tumors may vary according to the histological elements present. These tumor markers, together with the neuroimaging features discussed later, allow the histological subtypes of CNS GCTs to be assessed before surgery. As is the case for other CNS neoplasms, etiologic factors such as tumor location and patient age are also helpful for accurate diagnosis. As mentioned previously, the pineal gland is one of the most frequent sites for CNS GCTs. If a tumor is found in the pineal region in a teenage boy, it is highly likely to be a CNS GCT. Other tumors can arise in this region, but at a lower frequency in this age group. More detailed diagnosis should be made on the basis of neuroimaging features, together with tumor markers.

	β -hCG	α -FP
Germinoma	— ~ \uparrow	—
Mature teratoma	—	—
Immature teratoma	—	— ~ \uparrow
Teratoma with malignant transformation	—	— ~ \uparrow
Embryonal carcinoma	—	— ~ \uparrow
Yolk sac tumor	—	$\uparrow\uparrow\uparrow$
Choriocarcinoma	$\uparrow\uparrow\uparrow$	—

Table 1. Tumor markers and histological subtypes

2.1 MRI and CT features of CNS GCTs

2.1.1 Pineal tumors

For tumors in the pineal gland in children or young adults, differential diagnoses are limited. Although many CNS tumors can occur in this location, those that apparently arise within the pineal gland itself are limited. Many tumors, such as meningiomas, gliomas or ependymomas, can occur in the pineal region, but they extend from neighboring structures and do not arise in the pineal gland itself. Most pineal tumors in the true sense are CNS GCTs or pineal parenchymal tumors, i.e. pineocytoma, pineal parenchymal tumor of

intermediate differentiation, or pineoblastoma. All of these tumors can cause obstructive hydrocephalus due to compression to the aqueduct. Thus, the initial symptoms and neuroimaging finding of pineal CNS GCTs often reflect increased intracranial pressure due to hydrocephalus (Figure 3).

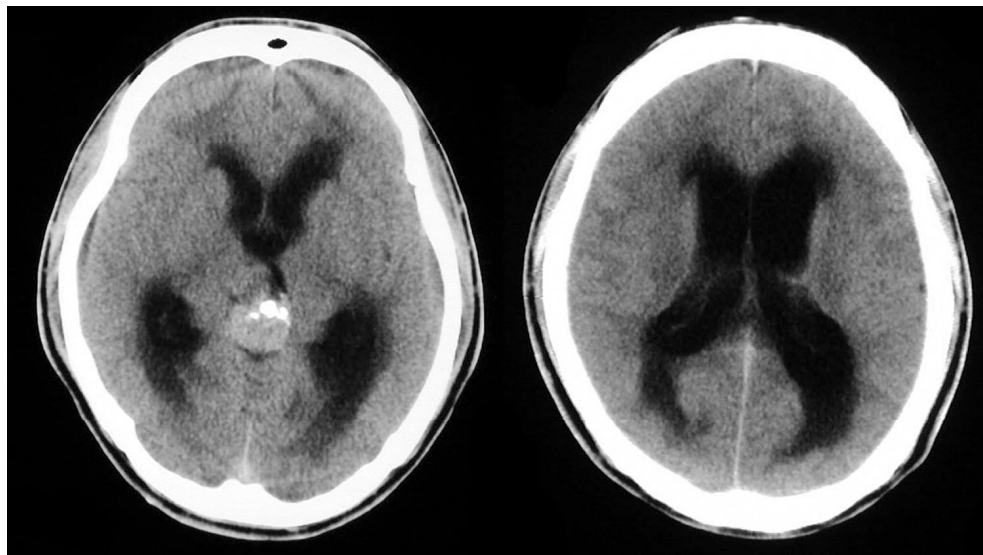


Fig. 3. Computed tomography (CT) scans of a pineal germinoma on admission. Marked hydrocephalus is evident together with the pineal mass.

Among CNS GCTs, germinomas and teratomas each show a peculiar pattern. Germinomas show slightly high to high density on plain (non-enhanced) CT scans. The border is clear where the tumor faces the cerebrospinal fluid space (cistern or ventricle), but somewhat obscure where the tumor faces the brain parenchyma. These tumors show marked homogeneous enhancement with contrast media [7-9]. Small intratumoral cysts may be present [9], and calcifications within the tumor are frequently evident [10, 11]. On T1-weighted MRI (the most basic MRI scanning), they appear as a well demarcated mass with a slightly low signal intensity. On T2-weighted images (which is another basic MRI scanning and in which tissues containing more water molecules show high signal) the germinomas show slightly high intensity (Figure 4) [9, 12-14]. Teratomas appear as heterogeneous masses, since they contain many histological elements [9, 12, 14]. CT shows that they are well demarcated, containing multiple small and large cysts and some calcifications. The entire tumor, or some part of it, may be well enhanced [9]. Teratomas sometimes contain fatty tissue, which is well detected by MRI, showing high signal intensity on both T1- and T2-weighted images. If such fatty tissues are detected by MRI, the tumor is highly likely to be a teratoma, or at least to contain a teratomatous component [9, 14]. On MRI, teratomas are well enhanced with gadolinium, except for cystic components (Figure 5). As mentioned above, teratomas may be benign or contain immature elements or malignant components. When the tumor's growth rate is high, perifocal edema may be detected on T2-weighted images [15].

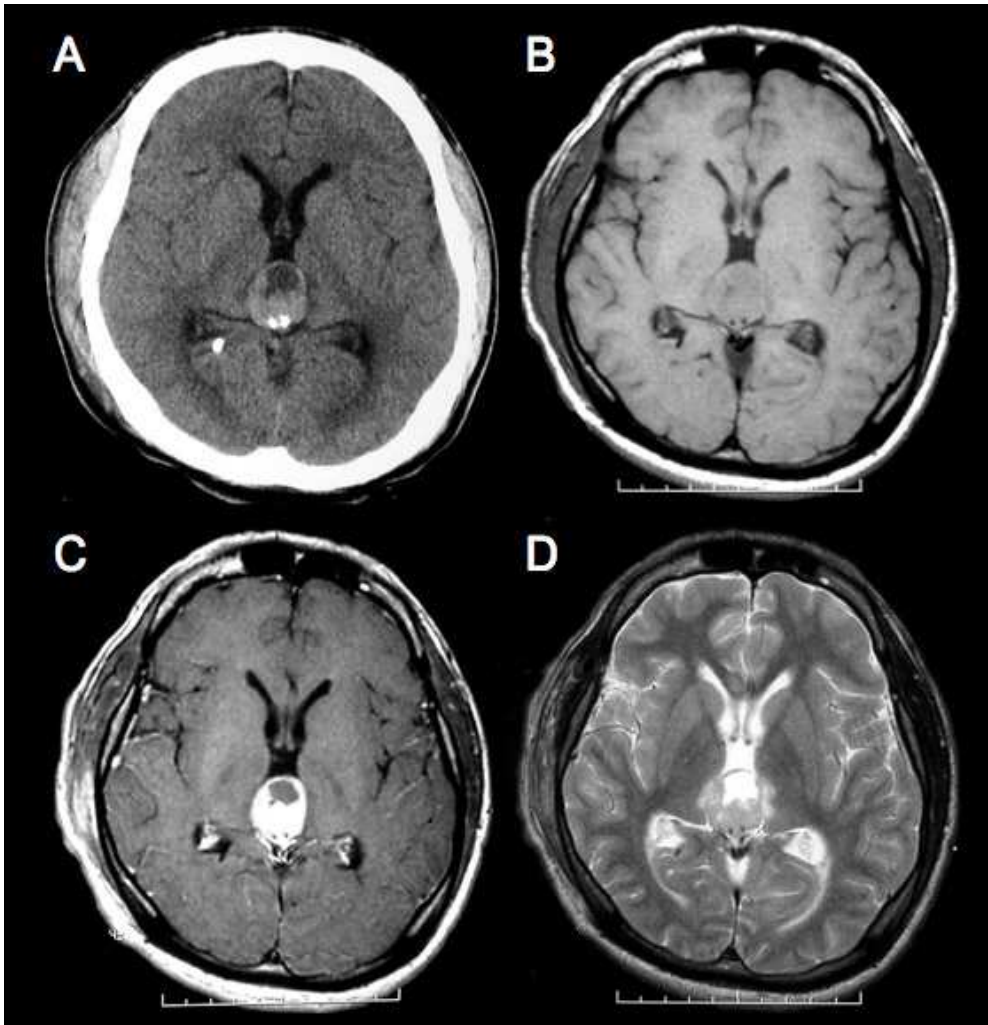


Fig. 4. Pineal germinoma in an 18-year-old boy. (A) CT scan shows a slightly high-density mass in the pineal region, together with a cyst and some calcifications. A ventricular drainage tube is inserted into the posterior horn of the right lateral ventricle. The tumor shows slightly low signal intensity on the T1-weighted image (B) and slightly high signal intensity on the T2-weighted image (D). The tumor is homogeneously well enhanced by gadolinium (C).

Other malignant subtypes are difficult to diagnose on the basis of neuroimaging features alone, but certain tendencies are evident for some tumors; yolk sac tumors tend to be irregular in shape, and unlike germinomas, show isodensity or slightly low density by non-enhanced CT [9]. Occasionally, the onset of choriocarcinoma may be accompanied by intracranial bleeding (Figure 6). In young adult or pediatric patients presenting with intraventricular hemorrhage, the possible presence of occult choriocarcinoma other than

cerebrovascular conditions such as arteriovenous malformation should be considered. As mentioned above, measurement of the serum β -hCG level is helpful in this situation. These malignant subtypes or mixed germ cell tumors with these elements are more aggressive than germinomas or teratomas, and thus often also have perifocal edema.

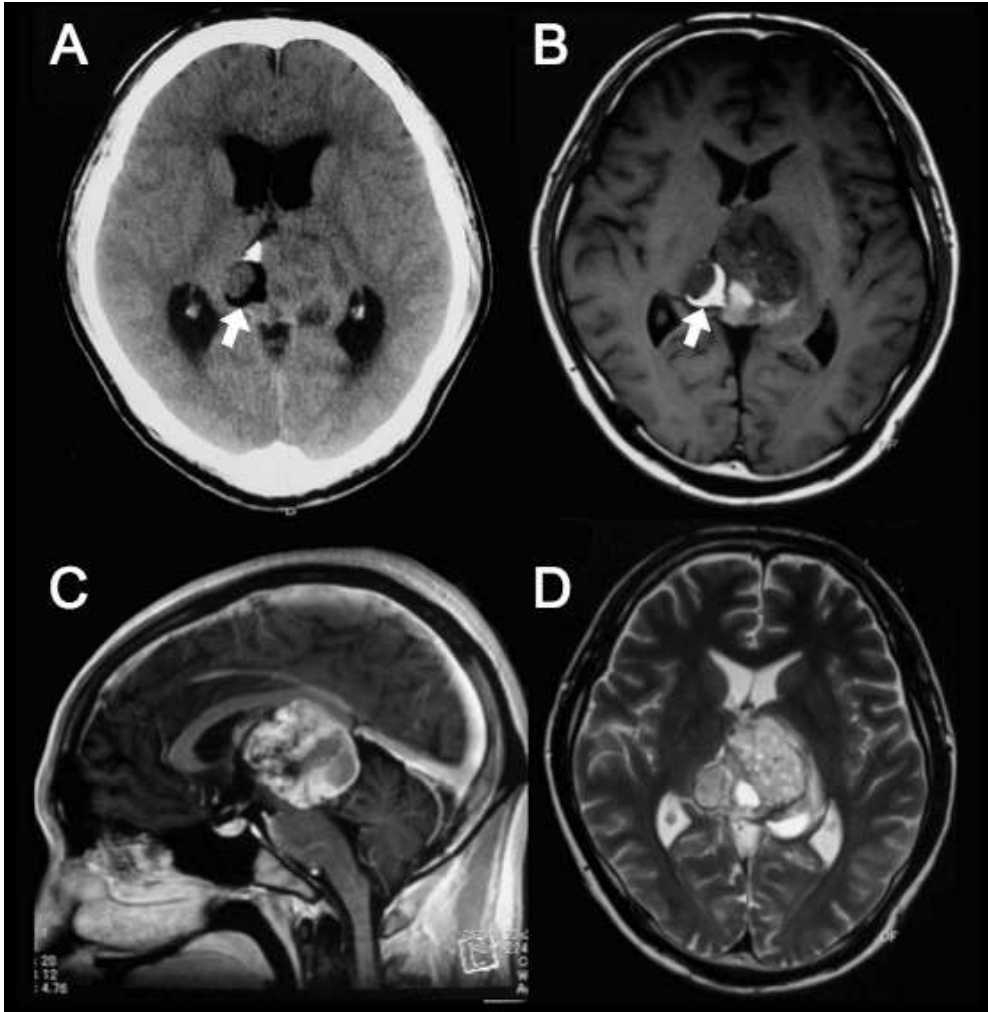


Fig. 5. Mixed germ cell tumor composed of immature teratoma and yolk sac tumor. The tumor contains calcification and fatty tissue. The low-density area evident on CT (white arrow, A) or the area of high signal intensity (white arrow, B) on the T1-weighted image indicates the presence of fatty tissue. The tumor is heterogeneously enhanced (C). The T2-weighted image also shows a heterogeneous pattern (D).

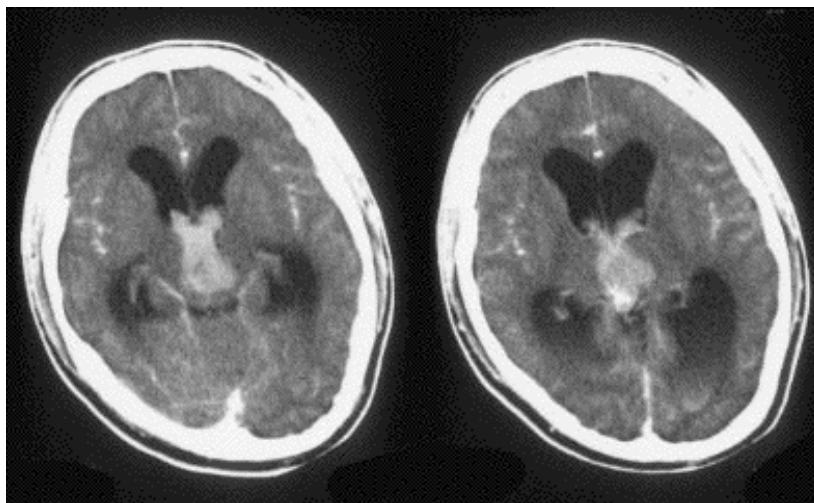


Fig. 6. A 16-year-old boy who was admitted in a comatose state. CT scans show intraventricular hemorrhage with hydrocephalus. The level of beta-hCG was markedly elevated. The diagnosis of choriocarcinoma was confirmed by biopsy three weeks later.

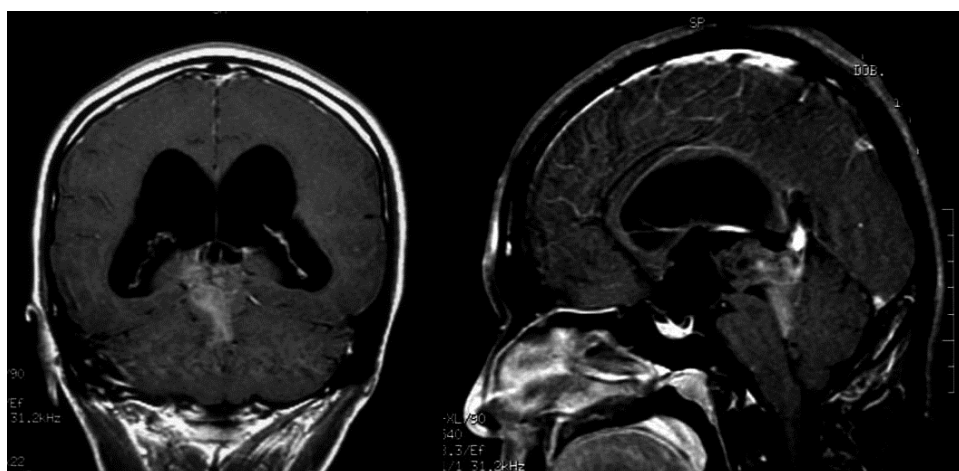


Fig. 7. A 26-year-old woman with a pineal parenchymal tumor showing intermediate differentiation. The tumor extends to the quadrigeminal and supracerebellar cisterns.

Pineal parenchymal tumors are rare, and reports on their neuroimaging features are limited. However, CT scan can often detect calcifications, and the pattern differs from that of germ cell tumors. Such calcifications correspond to an “exploded” pattern of preexisting pineal calcification, whereas those of germinomas are included within the tumor [10]. On MRI, differentiation between CNS GCTs and pineal parenchymal tumors is difficult [15]. For example, pineocytoma also shows slightly high signal intensity on T2-weighted images. However, pineoblastoma, the most malignant form of pineal parenchymal tumor, shows a

signal that is iso-intense with gray matter on T2-weighted images, and invades into surrounding structures [15]; perifocal edema may also be present. If a tumor extends expansively to fill the quadrigeminal to supracerebellar cistern frontal to the cerebellar culmen, it may be a pineal parenchymal tumor rather than a germ cell tumor (Figure 7) [13, 15].

2.1.2 Tumors of the neurohypophyseal region

The neurohypophysis or suprasellar area is the second-most frequent site for CNS GSTs. The basic neuroimaging characteristics of CNS GSTs in this location are not different from those of pineal ones in terms of density or signal intensity, enhancement pattern, and so on (Figure 8). However, calcification demonstrated by CT is somewhat different, as there is no “preexisting pineal calcification” in this area. Other tumors such as pituitary adenoma and craniopharyngioma, or inflammatory diseases such as Langerhans cell histiocytosis (LCH), can arise here [16, 17]. Most CNS GCTs arise from the pituitary stalk or hypothalamic area, whereas pituitary adenomas occur within the pituitary gland itself. Moreover, pituitary adenomas are relatively rare in the pediatric population. For these reasons, there is generally no problem in recognizing pituitary adenomas. However, differentiation between CNS GCTs and some of the other tumors mentioned above is sometimes not so easy. Any tumor showing multiple cysts and calcifications in this area might be a teratoma or a craniopharyngioma [18]. However, teratomas arise more often in the pineal region than in the neurohypophysis. Matsutani et al. reported that among 153 CNS GCTs, only 4 teratomas arose in the neurohypophyseal region.[2]. The incidence of CNS GCTs in the pediatric population is 15% or less [1]. Thus the frequency of neurohypophyseal teratoma among all pediatric brain tumors might be around 0.4%. In contrast, the incidence of craniopharyngioma in the pediatric population is around 9% [1]. Thus a tumor with multiple cysts and calcifications is 20 times more likely to be a craniopharyngioma. Inflammatory diseases in this location, for example LCH, are sometimes difficult to differentiate from small CNS GCTs [19].

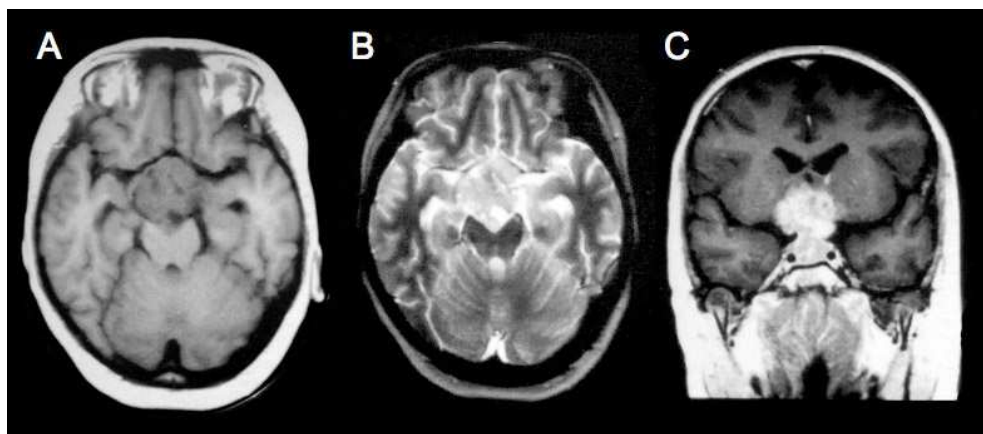


Fig. 8. Neurohypophyseal germinoma in a 12-year-old girl. A large tumor is evident in the basal cistern. The tumor shows slightly low signal intensity on the T1-weighted image (A) and slightly high signal intensity on the T2-weighted image (B). A coronal image after enhancement shows that the tumor is well enhanced.

Sometimes “bifocal” tumors arise in the neurohypophysis and pineal region (Figure 9). Most of these tumors are germinomas [20], but other histological subtypes of CNS GCT have also been reported [21]. As other central nervous system tumors rarely present this “bifocal” pattern, it is strongly suggestive of CNS GCT, especially germinoma.

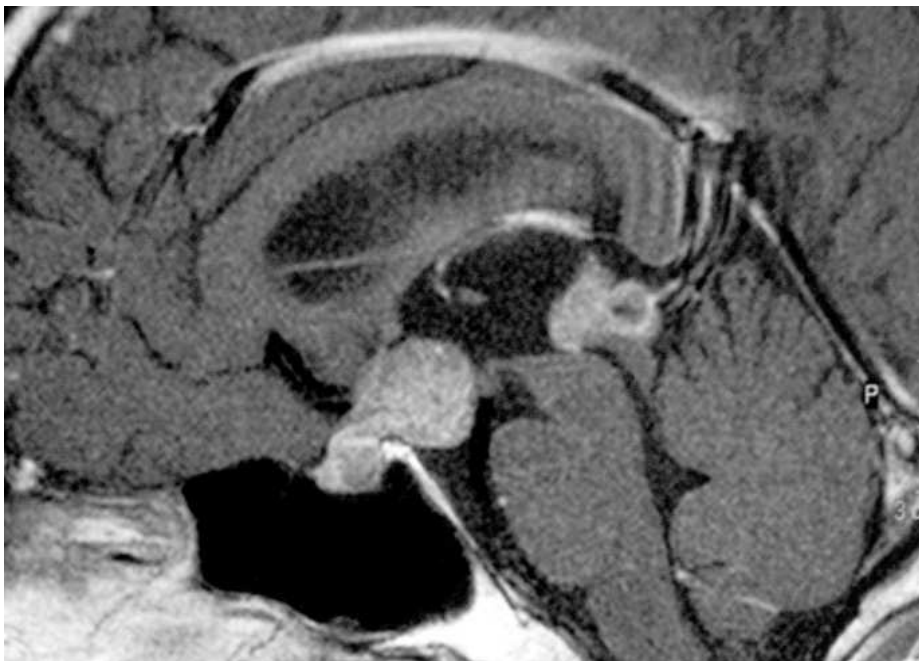


Fig. 9. A “bifocal” pattern germinoma is demonstrated on an enhanced sagittal image.

2.1.3 Other locations

Although CNS GCTs sometimes affect the basal ganglia, the neuroimaging features of GCTs in this location differ from those at other locations. Most CNS GCTs affecting the basal ganglia are germinomas, and are invasive. They show no mass effect or enhancement, initially [22-26]. Slightly high signal intensity on FLAIR or T2-weighted images is sometimes the only prominent finding. Thus, diagnosis at this stage is often difficult, and may be delayed even if a patient has undergone neuroimaging at an earlier stage. Later, the tumor may show exhibit a mass effect, enhancement, or even cysts. Tumor invasion to the pyramidal tract can cause hemiparesis. Hemiatrophy of the cerebral peduncle due to pyramidal tract impairment can be observed in patients with long-standing neurological symptoms (Figure 10) [24].

2.1.4 Spinal images

Occasionally, but not rarely, a tumor may show dissemination via the cerebrospinal fluid at initial presentation (Figure 11). Therefore, once a CNS GCT is suspected, enhanced MRI of the whole spine should be conducted.

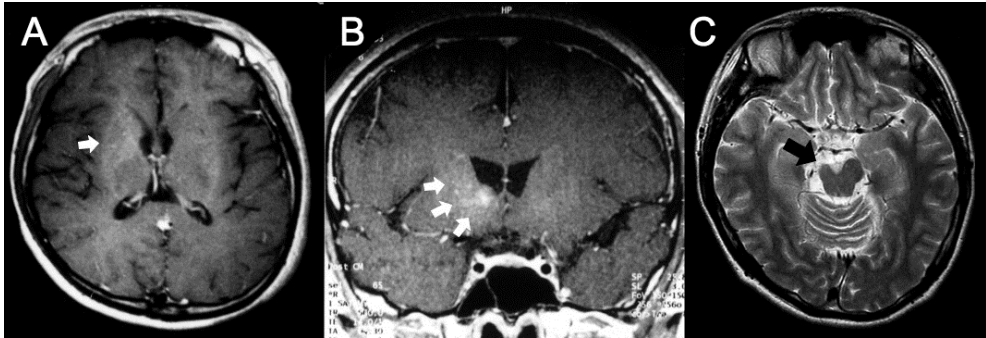


Fig. 10. Germinoma in the basal ganglia of a 21-year-old man. A gadolinium-enhanced MR image at initial presentation was diagnosed as normal, although the patient presented with slight left hemiparesis (A). Eight months later, enhanced MRI demonstrated slight enhancement (B), and biopsy confirmed the diagnosis of germinoma (B). The tumor was well controlled after chemo-radiotherapy, but the patient remained hemiparetic. Hemiatrophy of the cerebral peduncle was evident after 12 years (C).

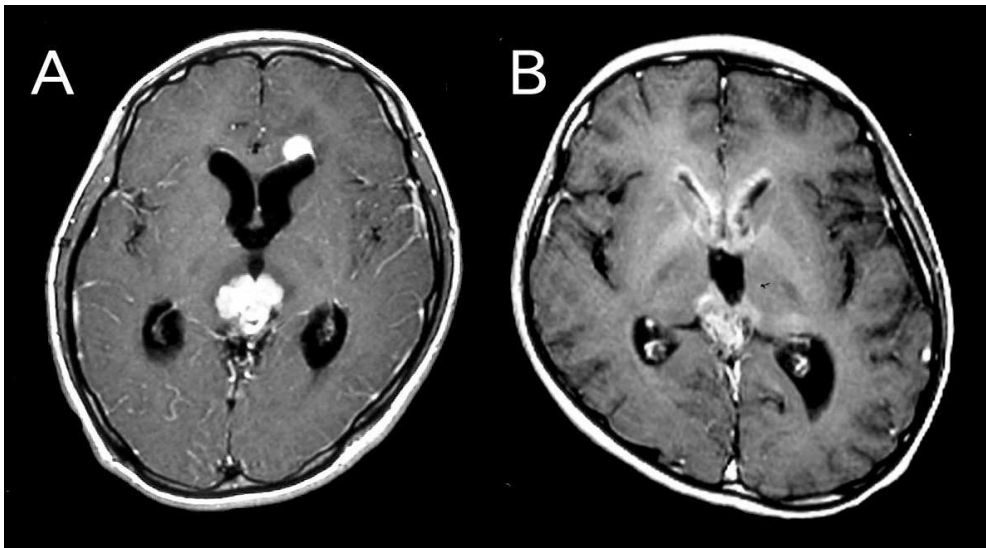


Fig. 11. MRI scans obtained at initial presentation, showing dissemination along the cerebrospinal fluid or subpial space in an 18-year-old boy (A) and a 13-year-old boy (B).

2.2 Other modalities for neuroimaging of CNS GCTs

Recently, more advanced techniques such as magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) have been employed for diagnosing CNS diseases. Although reports on imaging of CNS GCTs using advanced techniques such as PET or MRS are limited, some have indicated the usefulness of these modalities for diagnosis or decision-making in a clinical setting. Increased tracer uptake has been demonstrated using both

methionine-PET (MET-PET) and fluorodeoxyglucose-PET (FDG-PET) in patients with germinomas. However, FDG-PET does not demonstrate increased uptake in some germinomas [22, 27]. For invasive tumors in the basal ganglia, Kawai et al. reported that they were able to decide an appropriate biopsy point on the basis of MET-PET images when the exact location of the tumor was unclear in usual MRI or CT images.[23]

On the basis of a MRS study, Harris et al. described that CNS GCTs have a high lipid and macromolecule (LMM) concentration in comparison with other brain tumors. They also detected taurine in germinomas and pineal parenchymal tumors [28]. Although at a preliminary stage of evaluation, MRS seems to be an interesting modality for diagnosis of CNS GCTs.

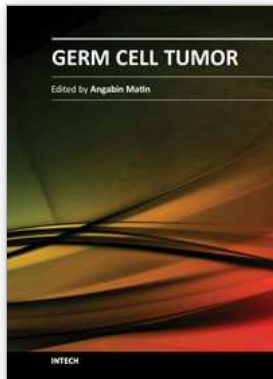
3. Conclusion

Through detailed interpretation of neuroimaging findings, together with tumor markers and other demographic clinical information, it is possible to determine the histological subtypes of CNS GCTs. With advanced imaging techniques, further improvement of diagnostic accuracy may be achievable, together with better understanding of the detailed biological characteristics of CNS GCTs.

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The book aims to provide an overview of current knowledge regarding germ cell tumors. It deals with the clinical presentations, treatment modalities, the biology and genetics of germ cell tumors in children and adults. Most chapters are focused on testicular germ cell tumors whose incidence has been increasing in young males. Included are reviews on the pathogenesis, risk factors, diagnosis and treatment regimens applied to precursor, pre-invasive lesions as well as to seminomatous and non-seminomatous germ cell tumors of the testes. In addition, a review is included on the diagnosis and current management options for intracranial germ cell tumors in children. Authors have also contributed articles on the genetics and epigenetics of germ cell tumor development in humans and in the mouse model system. This book will be of interest to scientists, physicians and lay readers wishing to review recent developments in the field of germ cell cancers.

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