Posterior Fossa Gangliogliomas

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51.1 Introduction

Gangliogliomas (GGs) are an uncommon primary neoplasm of the central nervous system. They account for 0.4–1.3 % of all intracranial tumors [51]. GGs are typically identified in adolescents and young adults. Eighty percent of the GGs occur, in fact, in patients younger than 30 years with a peak age of incidence between 10 and 20 years [13]. GGs are mostly a supratentorial with the majority of the tumors occurring in the temporal lobe. However, they may be found in any location of the central nervous system [31]. Infratentorial GGs are considered to be exceedingly rare. However, the development of modern pathological diagnostic techniques has suggested that these lesions might be more common than originally stated.

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51.2 Background

The term *ganglioglioma* was originally used by Loretz in 1870 and was later popularized by Perkins in 1926 to refer to an intracranial tumor composed of a mixed population of neoplastic astrocytes and atypical ganglion cells [27]. GGs were described by Cushing in his monograph published in 1927. In 1930, Courville correctly acknowledged the mixed histological composition of mature ganglion cells and glial cells of varying proportions and degrees of differentiation [11]. The first descriptions of infratentorial GG go back to 1911 with Pick and Bielschowsky [17]. Later Foerster and Gagel in 1932 provided the first documented reports of medullary GG [17].

51.3 Epidemiology of Infratentorial GG

The actual incidence of GG is difficult to evaluate with data varying from 0.4 to 7.6 according to the type of series (pediatric series or series comprising patients of all ages) [[31, 51]; Idlar]. According to Zulch and Cushing, these tumors are extremely rare. Indeed, in their reports, GG accounted for 0.4 % and 0.3 % of all brain tumors, respectively [51].

GGs are prevalently located within the supratentorial compartment, the temporal lobe being most commonly affected, followed by the parietal and frontal lobes [13, 29, 31, 51]. The infratentorial location of GG, both within the cerebellum and the brainstem, is rare, with few anecdotal cases reported in the literature [43]. The brainstem location has been more frequently described than the cerebellar one (SSA, CDR). In 1984, by reviewing the literature, Garcia and coworkers [19] found only 14 cases, and more recently, in 2001, Lagares et al. [32] reported 31 cases of brainstem GG in patients of all ages. Lang and associates [33] in their series on GG found among 58 cases from 3 months to 66 years of age an infratentorial location in 9. To date, 41 cases of infratentorial GG have been described in children. Within posterior fossa lesions, the proportion of GG remains low. In the series by Chang and associates, among 133 posterior cranial fossa tumors, only 1 case of GG was described [9]. In 2001, Farmer et al. [16] found only three cases of GG in their 10-year review of brainstem gliomas. Similarly in 2003, Goncalves-Ferreira and coworkers [22] identified one case of GG in their series of 30 cases of focal brainstem expanding lesions. The age at presentation of infratentorial GG shows a wide range, beginning from 2 weeks to 59 years in brainstem GG and from 11 weeks to 60 years in cerebellar tumors. In general, the tumor affects mostly patients younger than 30 years with a peak age of incidence between 10 and 20 years [31, 32, 51].

No significant preference for sex or ethnicity has been reported.

51.4 Clinical Presentation

The clinical history of infratentorial GG before diagnosis is generally short compared to GG within the cerebral hemisphere (6 years and 1.25 years, respectively [33]). In children, however, the duration of symptoms before diagnosis can be as long as 7 years [3].

The clinical presentation of infratentorial GG depends on the structures involved. Pure cerebellar forms are rare. In most of the cases, the GGs are located within the brainstem or cerebellar peduncles (brainstem or transitional forms [38]).

Such brainstem location is the most common within the posterior cranial fossa. It is commonly revealed by focal motor and sensorial long pathway impairment and/or cranial nerve deficits, namely, hearing loss, intractable facial pain, hemifacial seizures, and hemiparesis. Cerebellar hemispheric signs and gait disturbance may also contribute to the picture. Headache is common [1, 3, 5, 14, 17, 24, 32].

More rarely, brainstem GGs may cause respiratory problems, syncope, and even sudden death [17, 32]. In fact, many of the brainstem GGs reported in the past were only detected by the postmortem.

Cerebellar GGs are more often hemispheric and present with slowly progressive cerebellar signs, eventually associated to gait disturbance. There are some reports describing epilepsy of cerebellar origin in patients with cerebellar GG [8, 24, 36]. Whether the cerebellar tumor initiates the seizure or simply lowers their epileptic threshold is still debated. Although the exact mechanism for the epilepsy arising in the cerebellum is not known, invasive electrophysiologic monitoring with depth electrodes has confirmed the cerebellum as the site of seizure origin [24]. It is thought that seizures arise in the cerebellum to subsequently generalize by involving the cortical surface secondarily [8, 24].

In spite of the location, hydrocephalus is rarely found in children with posterior fossa GG.
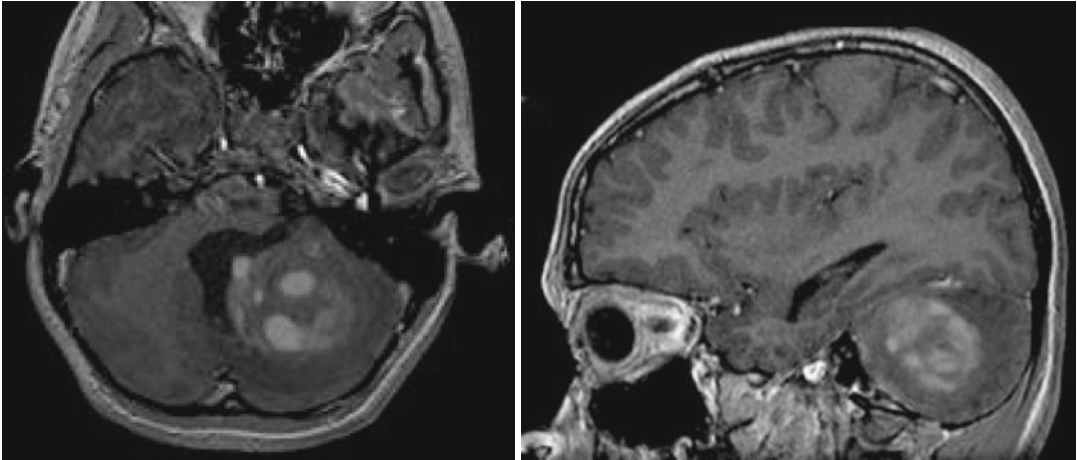
Fig. 51.1 Axial and sagittal post-gadolinium T1-weighted images show a typical aspect of ganglioglioma in the left cerebellar hemisphere with a mass effect. The enhanced-T1 image demonstrates patchy enhancement

51.5   Radiology Findings

On CT scans, most of GG present as masses with low density [[5, 31, 51]]. Calcifications reported in the literature in 20–50 % of the cases [[5, 31, 51]]. The degree of contrast uptake is variable, with 16–80 % of the patients showing an obvious enhancement [31]. Occasionally, GG can escape CT recognition consequently delaying the correct diagnosis (SSA). Even though MR imaging has proved to be more sensitive in identifying GG, the MR appearance is also variable and often nonspecific, with a spectrum of signal intensity ranging from hypointense to hyperintense on short MR images and hyperintense relative to the gray matter on long TR images [5, 31]. GG may appear cystic, solid, or mixed with nonspecific gadolinium enhancement [51]. The imaging features of infratentorial gangliogliomas seem to differ from those of a supratentorial location. The lesion is heterogeneous on imaging, appearing hypointense on T1-weighted images and hyperintense on FLAIR or T2-weighted sequences. In addition, the tumor seems often infiltrating with mass effect. In the majority of cases, the pattern of contrast enhancement on the T1-weighted images

consists of small, patchy areas of enhancement. Tumor enhancement is in fact very common in infratentorial GG [3], whereas in other location it varies greatly [13]. The pattern of enhancement observed in infratentorial GG is often relatively specific when showing areas of patchy enhancement within the tumor mass as opposed to supratentorial gangliogliomas that often appear as a delineated uniformly enhancing mass. The lesion appears thus as a dysplastic infiltrating lesion with some enhancing areas (Fig. 51.1). Cystic components have been reported in 30–57 % of the cases [3, 7, 23]. In posterior fossa, the cystic aspect might remind that of a pilocytic astrocytoma (Fig. 51.2). Although the tumor usually appears as an intra-axial avascular mass, extra-axial or vascular presentation may occur too [[2]] (Fig. 51.3).

51.6   Histopathology

51.6.1   WHO Definition

Gangliogliomas belong to the group of glioneuronal tumors, morphologically characterized by a biphasic population of neuronal ganglion cell and
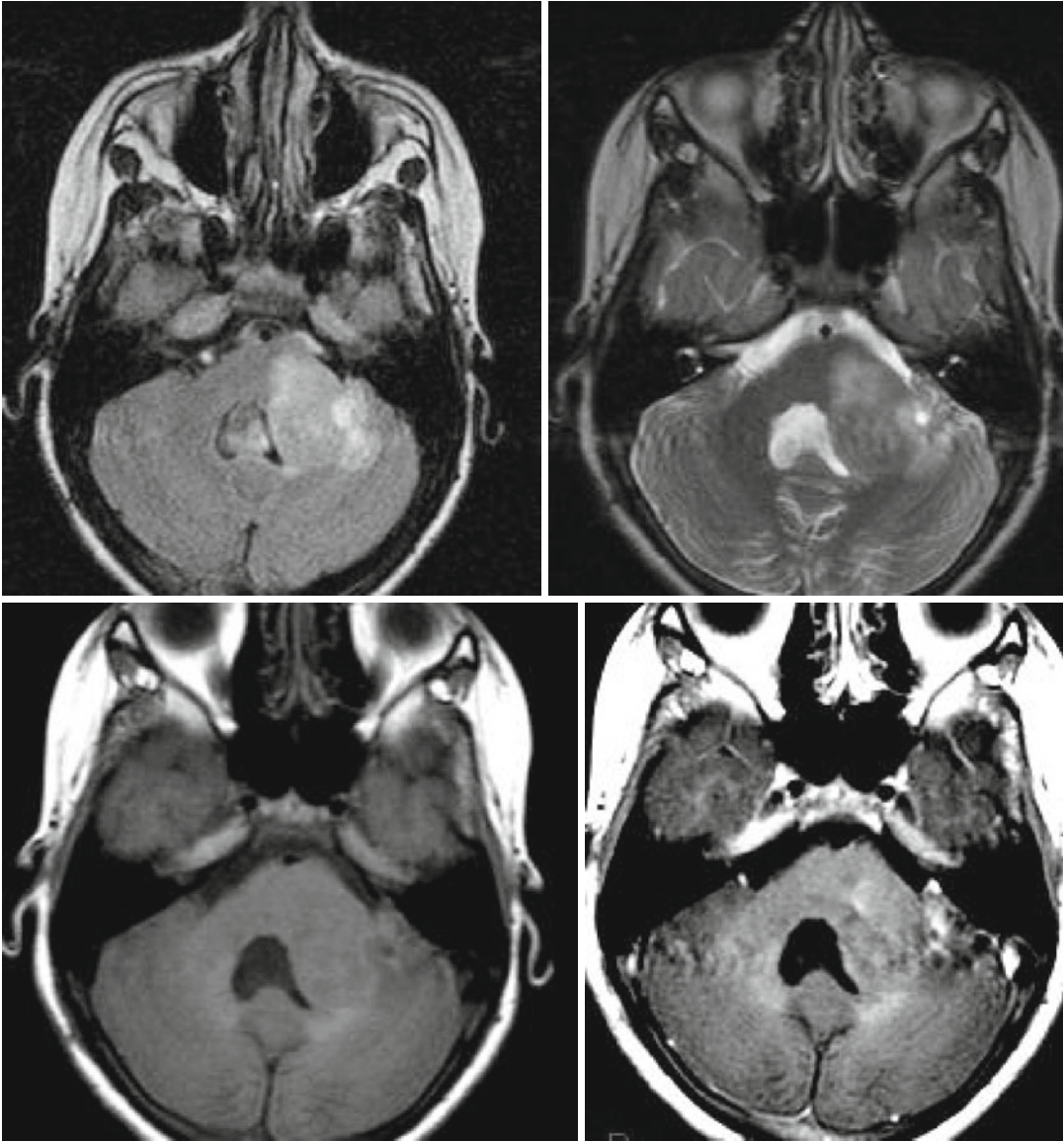
Fig. 51.2 FLAIR, T2, T1, and post-gadolinium T1 axial images show that the lesion is heterogeneous on imaging, appearing iso-intense on T1-weighted images and hyperintense on FLAIR or T2-weighted sequences. The tumor is infiltrating and mass effect was noted

glial cell components. According to the WHO 2007 classification, GGs correspond to benign WHO grade I. Some rare GGs presenting the same anaplastic features found in aggressive gliomas are considered WHO grade III. Criteria for defining GG grade II have been not yet established (ref [4]).
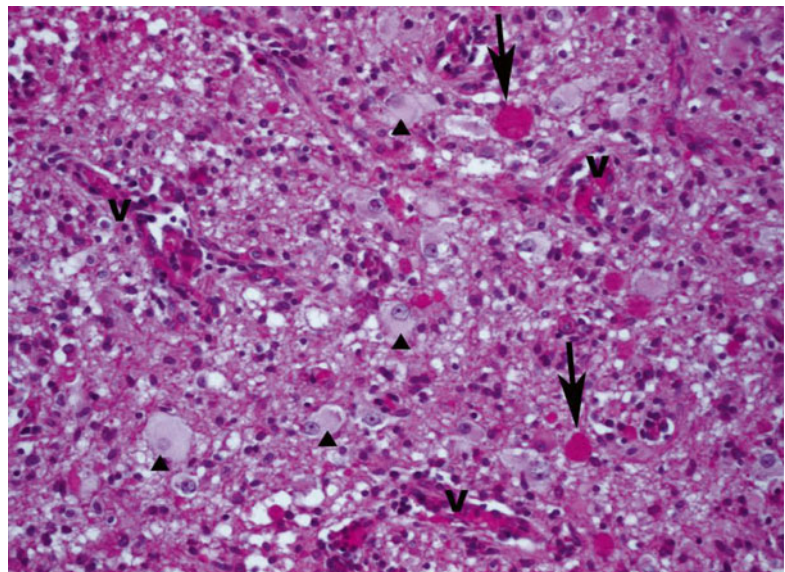
51.6.2 Pathological Findings

GGs are characterized by a mixed glioneuronal phenotype usually composed of a major glial morphotype associated with a neuronal ganglion cell component (Fig. 51.4). The histopathological identification of GG is notoriously challenging

because both glial and neuronal populations may exhibit marked phenotypic heterogeneity and distribution. Consequently, GG morphological spectrum can range from a predominantly glial phenotype with exceptional ganglion cells to predominantly neuronal population. Glial elements are usually piloid astrocytic, but the glial cells

Fig. 51.3 Axial post-gadolinium T1-weighted images show a cystic tumor with an enhancing solid nodule

can also present with an oligodendroglial, clear cell, gemistocytic, or ependymal morphology [4, 6, 37, 49]. Ganglion cells are characterized by their abnormal noncortical localization and distribution as well as by cytomegaly, bizarre shape, vesicular nuclei, and abnormally aggregated Nissl substance. All these criteria are not always associated. Consequently, a broad neuronal spectrum may be observed, leading to potential discrepancies between true neoplastic ganglion cells and dystrophic residual neurons, particularly in anatomic areas containing pyramidal or large neurons as it occurs in temporal or brainstem structures. Binucleated or multinucleated neurons are pathognomonic but unfortunately rare and heterogeneously distributed. Additional histopathological features such as Rosenthal fibers, eosinophilic granular bodies, perivascular lymphoid infiltrates, and abundant capillary networks with many parallel capillaries are also encountered frequently. These nonspecific features may alert and motivate a careful analysis of all the samples to search for a ganglion cell component. Desmoplasia (connective tissue component intermingled with glial lobules) is a common associated feature and should not be interpreted as an aggressive metastatic leptomeningeal extension. Histologically, as compared to pilocytic astrocytoma, GGs are

Fig. 51.4 Histological appearance of a typical ganglioglioma with double neuronal and glial component composed many ganglion neurons (*arrowhead*) and accompanied by granular body (*arrows*) characteristic but nonspecific. Vasculature is unique with many parallel capillaries (V) surrounded by perivascular lymphocytic infiltrate

not frequently well defined from the surrounding brain structures. They are associated with areas of marked dysplastic and/or atrophic parenchyma, leading in MRI to pseudo-infiltrating images.

The immunohistochemical profile of GG reflects the mixed glioneuronal nature, and many neuronal routine markers (such as chromogranin A, synaptophysin, NF70, and NeuN) are heterogeneously positive in ganglion cells. It is important to note that all these markers are not specific to neoplastic ganglion cells and are also positive in normal residual neurons. As a consequence, neuronal markers should be interpreted carefully and comparatively, preferentially in areas of tumoral tissue or in desmoplastic areas. Recently, studies suggested that the oncofetal CD34 transiently expressed during early neural development is frequently expressed in GG [[6, 12]]. These intratumoral and peritumoral highly ramified CD34 immunopositive cells are encountered in 66–74 % of gangliogliomas and are negative or only exceptional in DNET, pilocytic astrocytoma, or the infiltrative areas of low-grade oligodendroglioma or astrocytoma. Although the exact nature of the CD34-positive cells is not known, it has been suggested that they represent a glioneuronal progenitor cell as the majority of CD34-positive cells co-localized with S100 protein and more rarely with neuronal antigens [[6, 12]]. Thus, CD34 represents a valuable marker for the diagnostic evaluation of GG. MIB-1 index is generally low with a mean value ranging from 1 to 2.7 % [34].

51.6.3 Molecular Findings

Nonconsistent and recurrent allelic alterations have been identified, but gain of chromosomes 5, 7, 8, and 12 and loss of chromosomes 9, 10, and 22 have been described too [26]. No TP53 mutation, PTEN mutation, KRAS or IDH 1 mutation, or EGFR amplification [15, 50] has been documented. Mutational analysis in the coding region of the tuberous sclerosis 1 and 2 genes (TSC1, TSC2) did not discover any mutation on genes involved in the Reelin pathway [34]. However, in the two past years, the pathogenesis of GG is moving up by the involvement of an aberrant mitogen-activated protein kinase (MAPK) pathway activation due to the identification of BRAF activating mutation [46]. The mechanism of MAPK activation seems to be different than in pilocytic astrocytoma (PA). Many recent studies have demonstrated gene fusions between KIAA1549 and BRAF in the majority of the PA, whereas BRAF activating mutation, particularly V600E, represents the genetic hallmark of GG [15, 34, 39, 45, 47]. These recent data, described in a small number of GG, need further translational studies particularly to establish the prognostic significance and more interestingly whether children with GG may benefit from inhibitors of the MAPK signaling pathway.

51.7 Differential Diagnosis

Two main groups of differential diagnoses should be considered:

1. Diffuse infiltrating gliomas containing residual trapped neurons. This possible "overdiagnosis" of GG is of importance as it can impact on the management and prognosis. Radiological and histopathological correlations may assist in distinguishing between these two entities. Diffuse gliomas present ill-defined margins on T2-weighted images without contrast enhancement, whereas GG is a more well-delineated, often cystic lesion. Furthermore, GG may present contrast-enhancing nodules. Unfortunately, reliable histopathological and immunophenotypical distinguishing criteria are scarce. Only binucleated neurons and CD34 extravascular positivity represent good arguments in favor of the neoplastic nature of the neuronal component.

2. CNS lesions containing ganglion cells: pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor (DNET), pleomorphic xantho-astrocytoma (PXA), cortical dysplasia, Lhermitte-Duclos disease, and desmoplastic infantile ganglioglioma (DIG). The differential diagnosis with this type of tumors is particularly important. PA, DNET, and focal cortical dysplasia are stable lesions, while GG can undergo malignant transformation, even though rarely.

Pilocytic astrocytoma: The differential diagnosis with PA may be particularly difficult as the most frequent glial component of GG is morphologically piloid and frequently associated with Rosenthal fibers and eosinophilic granular bodies. Clinical and radiological considerations are of little help because these two entities are very similar with regard to the natural history and neuroradiological findings. The lack of CD34 immunoreactivity is a consistent finding in pilocytic astrocytoma and can help in the distinction between the two entities [6]. More recently, tandem duplication in chromosome band 7q34 with a KIAA1549-BRAF fusion has been described specifically in PA but not in GG [15, 39, 45, 47].

Dysembryoplastic neuroepithelial tumor (*DNET*): Complex form of DNET containing the specific glioneuronal element (GNE) but presenting frequently a neuronal component as intracortical lesion should be considered as DNET even if focally a dysmorphic neuronal component is observed. The recent findings of the absence of BRAF V600E mutation in DNETs and overlapping cases of DNET/GG support this idea [15]. The more challenging differential diagnosis is represented when the GNE is damaged, rare, or fragmented in biopsy or small specimens. In this situation, multiple histological sections and CD34 immunostainings can be useful as CD34 positivity is more frequent in GG than in DNET [12].

Pleomorphic xantho-astrocytoma (*PXA*)*:* PXA corresponds to an astrocytic neoplasm grade II, characterized by pleomorphic and lipidized astrocyte, according to the WHO 2007 classification. However, this entity presents numerous clinical, radiological, and histological features overlapping those of GG. All the key histopathological features characterizing PXA could be encountered in GG, namely, granular bodies, perivascular lymphocytes, and dense reticulin fiber network. Moreover, PXA may express neuronal markers as well as CD34 with a variable frequency [20, 42]. The recent findings of BRAF 600E mutations in a subset of PXAs support the fact that GG, PXA, and DIG/DIA represent a same pathological spectrum, containing more or less ganglion cells or desmoplastic features [15, 18].

51.8 Malignant Transformation and Prognostic Factors

Histological grading of GG is still controversial. In particular, criteria for grade II have not been defined in the last WHO 2007 classification. It is important to note that the classical criteria used for purely astrocytic adult gliomas have been applied to GGs. A specific and dedicated GG grading system is thus challenging due to the rarity of grade II or grade III GG, estimated to, respectively, 10–2 % of the cases [35]. In a large series of 203 GGs, a 3-tiered grading system was found to be statistically significative. The authors found a 5-year OS in grade II estimated at 79 % versus 53 % for the grade III [35]. In the HIT-GBM database, the 5-year overall survival of GG grade III was comparable at 88 % [30].

A gemistocytic component, increased proliferative activity, increased cellularity, nuclear pleomorphy, and high MIB-1 labeling index may herald an adverse clinical course [40; Majores 2008]. However, these potential prognostic features should be better defined and further confirmed.

51.9 Management of Infratentorial GG

51.9.1 Surgical Management

The treatment of choice for gangliogliomas is total macroscopic excision whenever possible [3, 23, 27, 33]. Total removal is associated with the highest probability of a long-term disease-free survival.

Unfortunately, infratentorial gangliogliomas are amenable to total excision only when the tumor is confined to the cerebellum. The excision is often incomplete if the tumor extends to the cerebellar peduncle and partial in practically all cases of brainstem involvement. Despite the difficulties that might be encountered during the removal of such lesions in these particular locations, surgery should still be considered as first treatment. It is worth to note that the removal of the enhancing portion of the tumor can result in a long event free survival even in the absence of any further treatment. In patients with residual

nonenhancing tumors, no evidence of tumor progression or enhancement has been reported, with a follow-up of at least 2.5 years [3].

Because of the characteristics of the tumor, however, a postoperative neurological deterioration has been reported in about 30 % of the cases with infratentorial GGs [33]. This elevated morbidity reflects the difficulties related to the infiltrative nature of these tumors and the risks of a too aggressive surgery within the brainstem. This morbidity can, in fact, be lowered by limiting the surgery to the enhancing component of the tumor [3].

51.9.2 Medical Treatment

There are only limited reports about the use of adjuvant therapy in patients with infratentorial GG. Scarce information is available from the experience with supratentorial GG as adjuvant therapy is commonly not utilized in these tumors usually amenable to radical excision, except in case of malignant subtypes. In case or residual tumors, adjuvant therapy has utilized either in the early postoperative period or at the moment of disease progression [29, 33]. The efficacy of adjuvant therapy to control tumor progression is, however, not clear from the literature. Its use may be also weighted by potentially fatal complications such as severe hematological aplasia [3]. Responses to chemotherapy of non-pilocytic glioma have usually been reported less frequently [21]. Frequently, chemotherapy alone fails to control on the long run the progression of the tumor requiring therefore additional radiotherapy. The absent or modest benefit of chemotherapy explains why it is not utilized even in case of residual tumor [3, 28, 48].

Radiotherapy has been used for treatment of some brainstem GGs, but, similarly, its usefulness has yet to be proven [32, 41]. The deleterious side effects on the developing nervous system have been a strong argument against the use of this treatment modality in children [29]. Moreover, some reports suggest that postoperative radiation may favor the malignant degeneration [25, 44]. Due to bias in patient selection for radiotherapy (more aggressive tumors, incomplete resections, early postoperative progressions, etc.), it is difficult to assign the transformation to the effect of radiation therapy. However, secondary tumors have been extensively documented after brain irradiation.

51.9.3 Prognostic Factors

Infratentorial gangliogliomas are generally benign tumors, but their natural course is difficult to predict.

Although infratentorial GGs frequently are resected only partially, the overall survival time does not seem reduced as compared with supratentorial GG where a more radical resection can be achieved [32]. Among brainstem tumors, gangliogliomas have a better prognosis than other brainstem gliomas [16].

Further, invasiveness on radiographic studies or anaplasia within a GG seems not to correlate with clinical outcome. However, the risk of recurrence is higher for brainstem and spinal GGs than for supratentorial GGs [5, 33].

Brainstem gangliogliomas have a fivefold increased risk of recurrence compared with equivalent tumors in the cerebral hemisphere [33]. However, not all incomplete resections ultimately show an evolution toward a recurrence. Among nine patients with a posterior fossa gangliogliomas with at least 75 % reduction in their volume after surgery, the tumor recurred in only two cases [33].

The presence or absence of contrast enhancing within the residual tumor seems to correlate with the risk of recurrence. When no postoperative enhancement in the residual tumor is found, no disease progression might be observed for many years [3]. Conversely, in patients with an enhancing residual lesion, tumor progression is common [3]. This finding implies that children with posterior fossa gangliogliomas may benefit from the removal of the enhancing component of the tumor, which consequently should be attempted when possible.

Conclusions

Gangliogliomas are rare and generally benign tumors that might occur in the posterior fossa. The MR images of these tumors show patchy

enhancement after gadolinium administration, in contrast to gangliogliomas found in the supratentorial compartment. A total macroscopic excision of the tumor is often impossible because of its location within cerebellar peduncle and/or the brainstem. Nevertheless, in some cases, the mere excision of the enhancing portion of the tumor may suffice to obtain long progression-free survivals. In cases of progression of the residual tumor, further excision may be effective in controlling disease progression. Chemotherapy is of scarce usefulness. The use of radiotherapy is limited in many cases because of the location of the tumor, the age of the patient, and the risk of malignant degeneration.

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