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CASE REPORT

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Therapeutic strategies and management of desmoplastic infantile ganglioglioma: two case reports and literature overview

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Abstract *Introduction:* Desmoplastic infantile gangliogliomas (DIG) are rare cerebral glioneural tumors usually occurring in early childhood. DIGs are generally benign although rare cases with poor outcome are known. Total resection, if possible, is the treatment of choice, without further adjuvant therapy. After incomplete resection, adjuvant chemo- and/or radiotherapy is generally applied, despite the potential negative side effects in such young patients. *Case reports:* We describe two girls with DIG, one who twice underwent subtotal resection at 3 and 5 months, the other who underwent total resection at 2 years. Neither had adjuvant therapy and there was no tumor recurrence. *Conclusions:* Our own experience and a review of the literature suggest that in most DIGs adjuvant therapy is not justified even after incomplete resection. After tumor recurrence a second surgical intervention should be considered instead of adjuvant therapy. An exception may be made for rare, deep-seated DIGs, which are more aggressive and have a poorer outcome.

Keywords Desmoplastic infantile ganglioglioma · Surgery · Adjuvant therapy · Outcome

Introduction

Desmoplastic infantile gangliogliomas (DIGs) are rare neoplasms that were first described by VandenBerg et al. in 1987 [19]. They typically occur in infants under 2 years. However, three cases of young adults (14–19 years) have also been recently reported, so that DIG does not seem to be a specific entity of infancy [5, 12, 20]. The huge size and relative lack of obtundation with such large masses suggest very slow growth, and the early age of onset has led to the speculation that this tumor could be of congenital origin [14]. At presentation the tumor is usually very large (up to 13 cm diameter), with associated cysts and attachment to the dura. The supratentorial region is preferentially involved, especially the frontal and parietal lobes, followed by the temporal [17], and rarely the occipital region. The symptoms, which usually appear soon after birth, include increasing head circumference, bulging fontanel, sunset sign, hemiparesis, and frequent seizures (irritation of surrounding brain or neuronal components may also be intrinsically epileptogenic). On MRI these tumors are radiologically characterized by a hypointense cystic mass with an isointense peripheral solid component on the T1-weighted scan that enhances with gadolinium; on T2-weighted images the cystic component is hyperintense and the solid portion is heterogeneous. The cysts are generally large, uni- or multiloculated, with clear or xanthochronic fluid. The solid superficial extracerebral part of the tumor is firm or rubbery in consistency, gray or white in color, and typically with dural attachment. Histologically, the tumors are characterized by a prominent desmoplastic stroma and mixture of neoplastic astrocytes and neuronal cells at varying stages of differentiation [14]. Mitotic activity is very low, and there is usually no necrosis. However, when present, mitoses and foci of necrosis are mostly restricted to areas with poorly differentiated neuroepithelial cells and they are not considered to be anaplastic

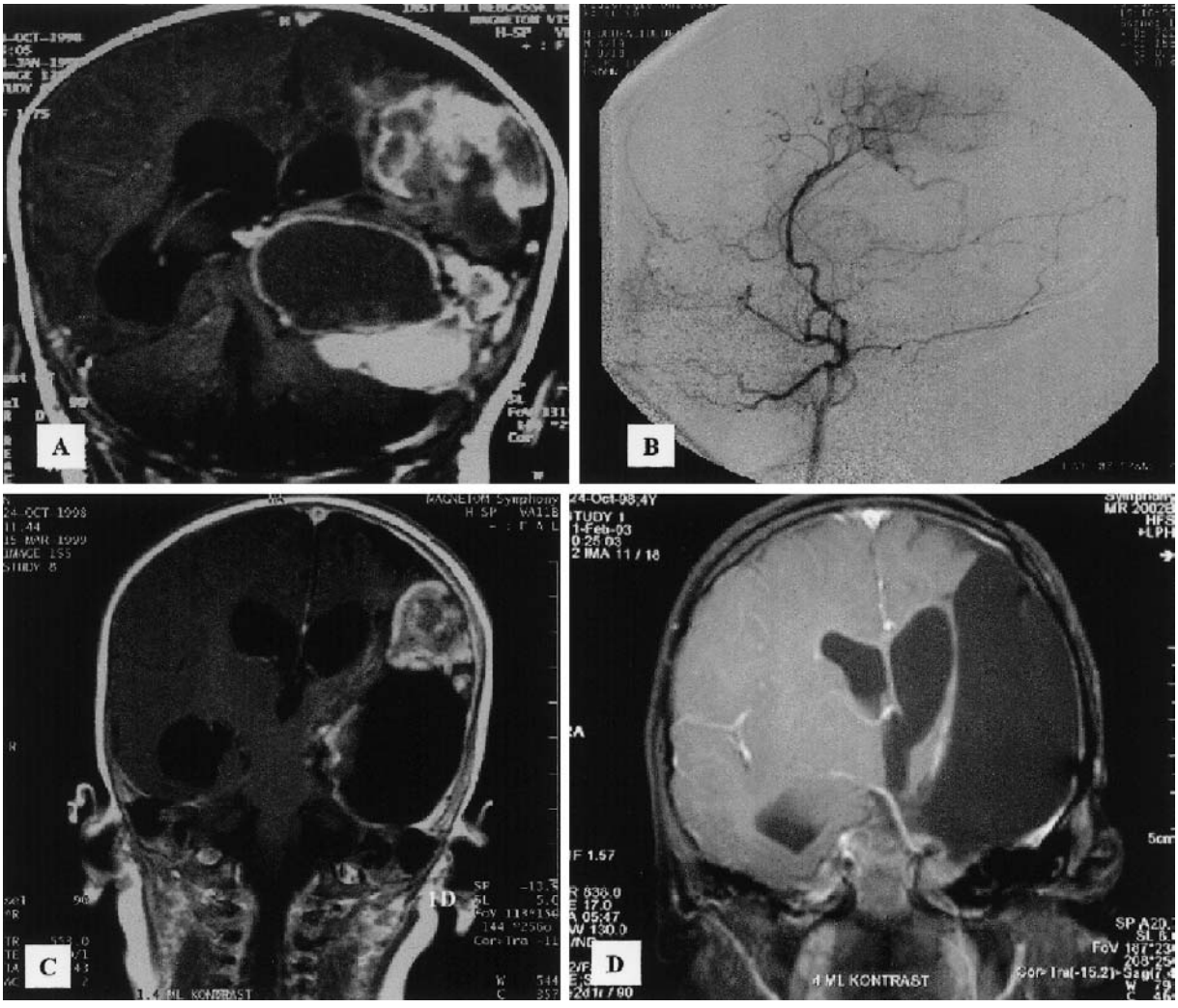

Fig. 1A–D Desmoplastic infantile ganglioglioma (DIG) in the left hemisphere of a 3-month-old girl. **A** Coronal post-contrast T1-weighted MRI scan showing a huge cystic tumor with typical dural attachment and midline shift. **B** Digital subtraction cerebral angiogram. **C** Coronal MRI scan after first operation with incompletely resected tumor. **D** Coronal post-contrast MRI scan 4 years after surgery without tumor recurrence

or malignant features. Recently, the formerly termed "desmoplastic infantile neuroepithelial tumors", either with or without ganglion cells, have been grouped collectively as "desmoplastic infantile astrocytoma (DIA) and ganglioglioma (DIG)", and included in common classifications of cerebral tumors [7, 11, 17]. Up to now about 60 cases of DIA/DIG have been described [14]. Whether DIA indeed represents a separate entity, or is just a form of DIG in which neurons have not been detected in the biopsied tissue, is a matter of debate [10, 14].

If possible, the preferred treatment of DIGs is total surgical resection. There is no unique practice in cases in which only incomplete resection has been carried out. Adjuvant chemotherapy and/or radiotherapy have been administered in most of these cases, with a maximal follow-up of 14 years. In this paper we describe two DIG patients, one with subtotal and one with total surgical resection, both of whom had a favorable outcome without adjuvant therapy.

Case reports

Case 1

Pregnancy was uneventful. At birth, this girl had a wide non-reactive pupil on the left side and paresis of the superior musculus rectus. These symptoms were interpreted as a birth trauma. Later hemiparesis developed on the right side. Neuropediatric consultation led to MRI, which revealed a large cystic tumor (7×5 cm) with inhomogeneous gadolinium enhancement, which completely filled the left hemisphere and caused a marked midline shift (Fig. 1A). The child was admitted to our Neurosurgical Clinic at the age of 3 months. The fontanel was plane, there was no pathological growth of the head, but clinically there was left-sided amaurosis, VII paresis on the left and hemiparesis on the right. Preoperative angiography showed a marked tumor blush, the

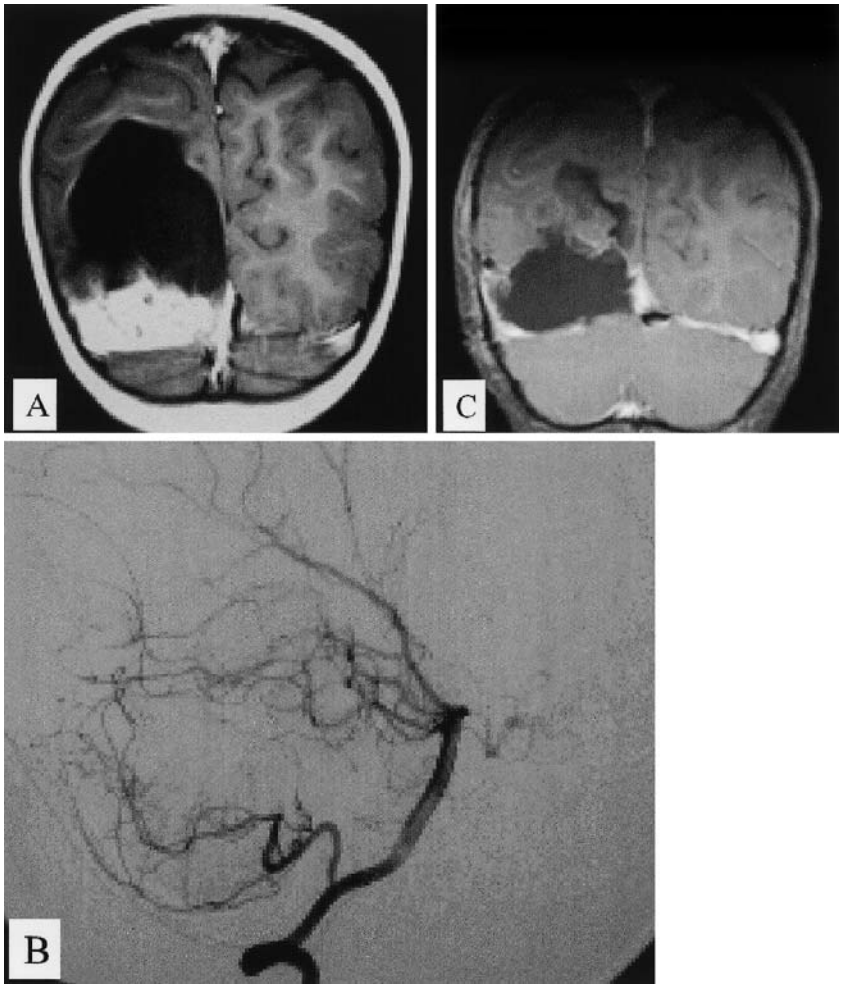

Fig. 2A–C Right occipital DIG in a 2-year-old girl. **A** Coronal post-contrast T1-weighted MRI scan with huge cystic tumor right parieto-occipital with extensive dural attachment on the tentorium. **B** Digital substraction cerebral angiogram. **C** Coronal MRI 3 months post-operatively without tumor recurrence

branches of the middle cerebral artery were displaced towards the front and there was a large vein draining into the left transverse sinus (Fig. 1B). The tumor, which was attached to the dura, was composed of multiple cysts and soft fleshy tumor tissue with calcification and signs of previous hemorrhages. Because of the attachment to the middle cerebral artery and branches of the posterior cerebral artery, the tumor could not be completely resected. The child recovered well, and postoperatively the hemiparesis was reduced, but the left-sided amaurosis remained. Epileptic seizures were successfully treated with valium infusions and a diabetes insipidus was substituted. A control MRI showed left fronto-parietal remains of the tumor , with a midline shift (Fig. 1C). In a second operation 2 months later some of the tumor and cyst were removed, but the rest attached to the arteries had to be left. Because of new cyst formation, a cysto-peritoneal drainage was inserted. Recovery was good, without any further neurological deficits. MRI control studies have been carried out at 3-month intervals. MRI 4 years after surgery showed no pathological contrast enhancement and no tumor recurrence (Fig. 1D).

Case 2

A 2-year-old girl, whose birth and family history were unremarkable, developed partial seizures on the left hand lasting for 30 min. She was admitted to our Children's Hospital, where again a partial seizure on the left side occurred (arm and leg). The neurological examination showed a homonymous hemianopsia on the left side, with no further neurological deficits. MRI showed a huge cystic, right parietal-occipital tumor with typical dural attachment and inhomogeneous contrast enhancement. There was little edema and a slight midline shift (Fig. 2A). Preoperative angiography showed a huge avascular, right parieto-occipital tumor with displacement of the right posterior cerebral artery towards the cranial. There was no tumor blush and no patency of the transverse sinus (Fig. 2B). The tumor could be completely resected. Because of the extensive dural attachment to the tentorium, resection was only possible step by step because of repeated bleeding. Postoperatively, the child recovered well, although the left homonymous hemianopsia persisted. Under phenobarbital medication no seizures occurred. In the 3-month follow-up there was no tumor recurrence (Fig. 2C).

Material and methods

Sections (4 μm thick) were prepared from formalin-fixed/paraffin-embedded specimens and were stained with hematoxylin and eosin, Masson's trichom and reticulin stains. Immunohistochemistry was performed using primary antibodies (monoclonal, unless otherwise specified): neuron-specific enolase (NSE; 1:8000; Dako, Copenhagen, Denmark), glial fibrillary acidic protein (GFAP, polyclonal; 1:200; Dako); synaptophysin (1:200; Dako), neurofilament (1:500; Bio-Genex, San Ramon, CA), epithelial membrane antigen (EMA; 1:50; Dako) and MIB-1 (1:800; Dianova, Hamburg, Germany).

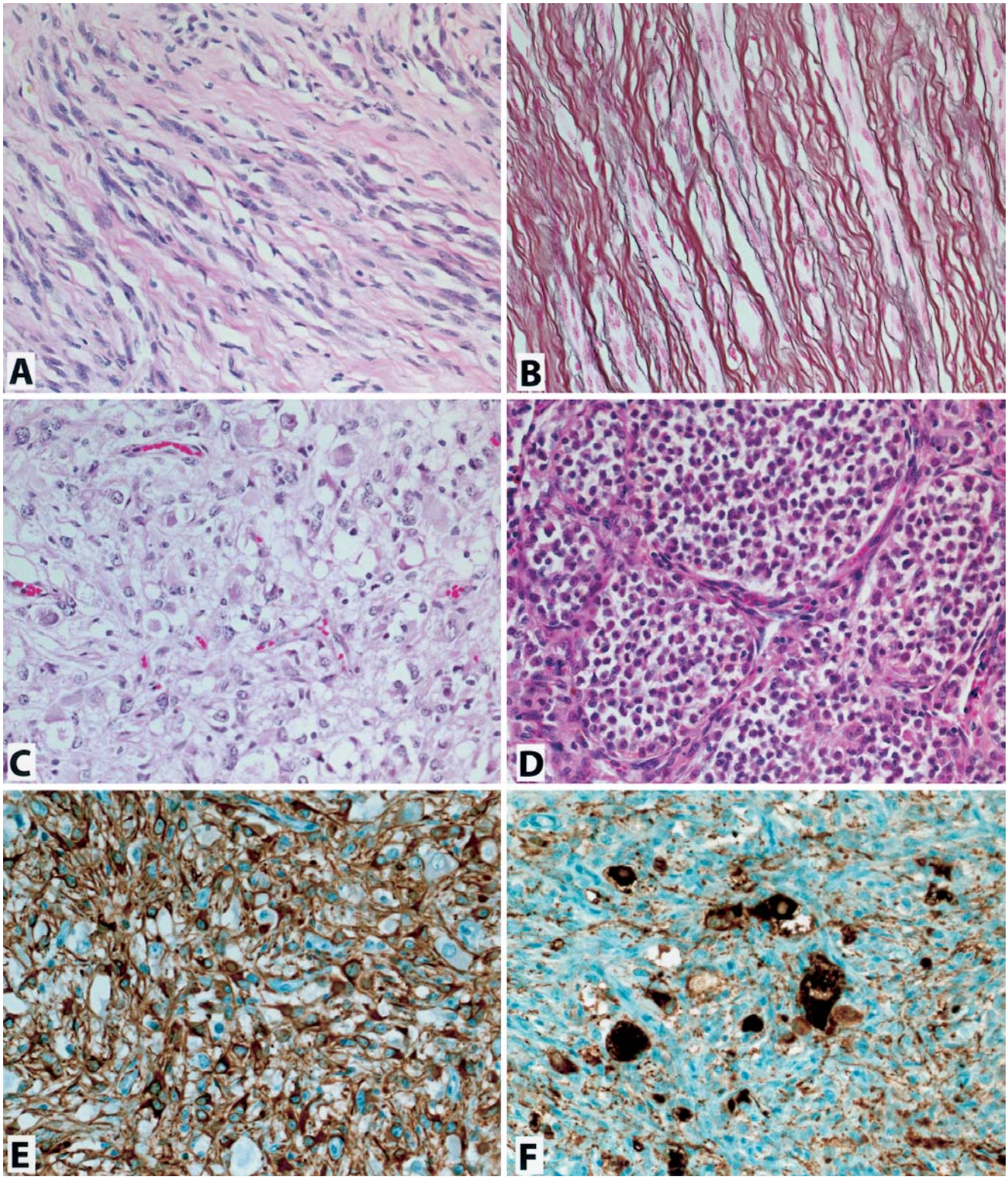

Fig. 3A–F Desmoplastic infantile ganglioglioma. Histology and immunohistochemistry. **A** Astrocytic tumor cells within marked desmoplastic areas. **B** Collagen and reticulum fibers surrounding tumor cells. **C** Tumor regions with many ganglion and ganglion-like cells. **D** Foci with aggregates of poorly differentiated neuroepithelial cells. **E** Glial fibrillary acidic protein immunoreactive neoplastic astrocytes. **F** Synaptophysin staining of ganglion cells and their process. **A–F** ×220; **A–D** H&E stains

Results

Histology

The multiple tissue fragments from both children showed largely similar histological features, consisting mainly of spindle, elongated tumor cells arranged in fascicles or in a storiform pattern (Fig. 3A), intermixed with collagen and reticulum fibers surrounding tumor cells (Fig. 3B). Some cells also resembled gemistocytes. In addition, larger ganglion-like cells were found in areas with scanty extracellular matrix (Fig. 3C). To variable extents, aggregates of poorly differentiated cells with small basophilic nuclei and minimal surrounding perikarya were present in both cases (Fig. 3D). Overall, however, cellularity and pleomorphism were moderate, mitoses were very rare and necrosis was absent.

Immunohistochemistry

Most of the spindle shaped cells in the desmoplastic stroma and the larger gemistocytes stained strongly for GFAP (Fig. 3E) while such an immunoreactivity was only found in a small subset of the poorly differentiated cells. The ganglion cells stained intensely for NSE and synaptophysin (Fig. 3F). Only a few small ganglion cell processes stained for neurofilament. All tumor cells were negative for EMA. In both tumors the mean MIB-1 proliferation rate was 1.5%.

The diagnosis of desmoplastic infantile ganglioglioma was confirmed by the Armed Forces Institute of Pathology (AFIP) in case 1 (AFIP Accession number 268098) and by the German Reference Center for Brain Tumors in case 2 (Accession number R-21517).

Discussion

Desmoplastic infantile gangliogliomas are rare cerebral tumors classified as WHO grade I with a generally excellent prognosis [1, 18, 19]. Many reports deal with histological, immunohistochemical, ultrastructural and/or molecular aspects and there is not much information about the management and therapeutic strategies of these tumors.

Although DIGs are considered to be benign tumors, some cases may exhibit at least focal histological features (e.g. aggregates of poorly differentiated cells with low to moderate mitotic activity, foci of necrosis) that may lead to the erroneous diagnosis of malignancy [11, 16, 19]. Since there is usually long-term survival after gross total resection, these changes are not considered to be anaplastic or malignant. Moreover, proliferation rates in DIGs are usually low with reported Ki-67 labeling indices ranging between 0.5 and 5% [1, 6, 20]. However, DIGs with overt anaplastic and malignant histological features, including necrosis with pseudopalisading of tumor cells, vascular proliferation, high mitotic rate and high Ki-67 labeling indices have also been described [1, 8, 9]. It is of interest that the outcome of these cases seems to be dependent on the location of the tumor. Thus the two anaplastic DIG cases with superficially located tumors reported by Kuchelmeister et al. [9] did not show recurrence after gross complete removal without further adjuvant therapy. In contrast, the unusual deeply seated anaplastic DIG case reported by De Munnynck et al. [1], presenting with intracerebral and pial metastases, showed an aggressive behavior after incomplete resection and adjuvant chemotherapy. A DIG case with deep tumor location but no anaplastic features was also reported, which finally led to death after incomplete resection and adjuvant chemotherapy [6, 13]. Similarly, there is a report of a deeply located desmoplastic infantile astrocytoma lacking anaplastic features, which presented with CSF dissemination and resulted in a poor outcome [15]. An additional deeply seated DIG involving the brainstem has recently been reported by Fan et al. [4]. Although there were no anaplastic features in this case, there was rapid tumor progression even after near-total resection and aggressive chemotherapy. A more favorable outcome for two deep-seated DIGs, one of them with anaplastic histological features, was reported by Duffner et al. [2]. In both cases more than 75% of the tumor could be resected and chemotherapy was applied. An overview of the literature about deep-seated DIGs/DIAs is given in Table 1.

Based on these findings we can conclude—most likely irrespective of the presence of histological anaplastic features—that the outcome of DIGs is at least partially determined by the tumor location. DIGs with a superficial location amenable to total gross surgical resection have a favorable prognosis, while DIGs with a deep location (possibly accompanied by CSF dissemination) show more aggressive behavior with a probably fatal outcome [4, 15].

At the moment there are no molecular genetic data that would enable us to predict tumor progression in DIGs [7].

The treatment of choice is complete surgical resection, if possible. Because most of the patients are very young, careful surgical planning and management are necessary. Two cases of death during surgery have been described [11, 16]. The extent of the surgical challenge and blood loss should not be underestimated in this population of patients. It is essential to know the relationship of the tumor to the sinuses and deeper vascular structures, and if this cannot be adequately seen on MRI it would be wise to perform preoperative angiography.

With reference to the Low Grade Glioma Study, we decided in our cases to carry out a follow-up with only 3-monthly MRIs without any additional therapy. No tu-

Table 1 Overview of cases of deep-seated DIG/DIA described in the literature

Case	Reference	Age, month	Sex	Presentation	Imaging	Treatment	Survival and follow-up	Histological anaplastic features
1	[1]	24	Girl	Macrocephaly, vomiting	MRI, large cystic tumor right hemisphere, pial enhancement along brainstem and optochiasmatic cistern, ependyma enhancement along IV ventricle, IV ventricle, nodular lesion hypothalamic region, spinal diffuse pial +dural enhancement, horacic +lumbar region	Partial resection, chemotherapy, tamoxifen	Recurrence 1 month after surgery, died 11 months later	Yes
2	[6, 13]	3.5	Boy	Macrocephaly, vomiting, emesis (2 months), tens fontanel, poor head control, lethargy (3.5 months)	CCT cystic + solid tumor ventral diencephalon, 4th vessel angiogram: avascular tumor, size 7 cm	Biopsy, chemotherapy (vincristine, actinomycin D)	Tumor progression, died after 6 years	No
3	[4]	6	Boy	Progressive left head tilt (10 days), lethargy, visual deterioration, motor skills	CCT + MRI solid + cystic mass right hemisphere with portion left ponto-mesencephalic	Partial resection, 1 week later near total resection, chemotherapy	5 months postoperative tumor ↑, 2 months postoperative tumor ↑ chemotherapy, MIB-1 rare	No
4	[2]	8	Boy	Seizures, vomiting	CCT large cystic tumor, left, temporal, deepest portion peduncle	Debulk (>75%), chemotherapy (12 months)	42 months, child alive and well, tumor stable	No
5	[2]	4	Boy	Right partial seizures (for 1 week)	CCT cystic (3×2 cm) and solid tumor (5×7×4 cm) left temporal, deep peduncle + adherent to inferior tentorium, myelogram, CSF test	Debulk (>75%), chemotherapy (24 months)	Postoperative right hemiparesis, III nerve palsy, 2 months later tumor ↑ →↓, 5 years free of disease	Yes
6	[15]	4	Boy	Macrocephaly, nystagmus	Large deep tumor suprasellar and hypothalamic region, 2 posterior fossa and 1 spinal canal (metastasis)	Biopsy, partial resection	No	

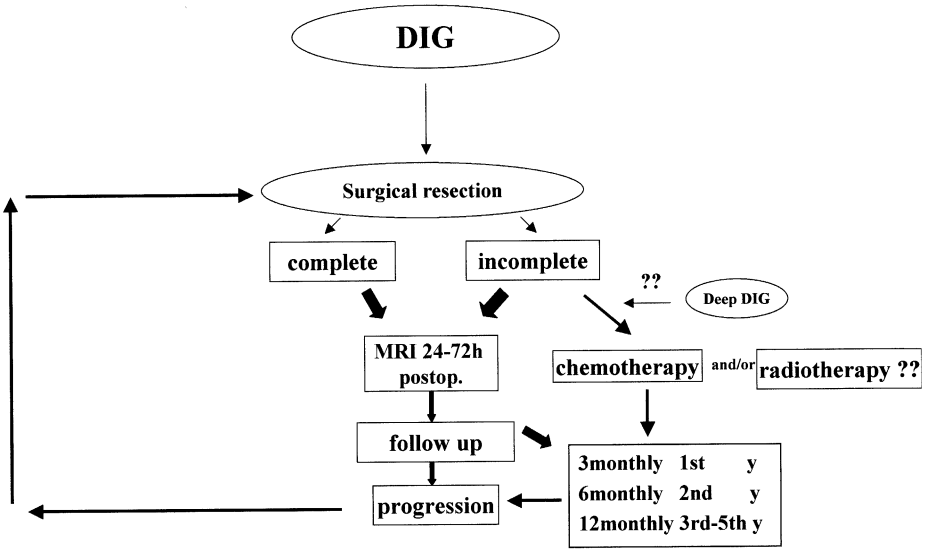

Fig. 4 Therapeutic plan for desmoplastic infantile ganglioglioma

mor recurrence was seen in either case 1 with subtotal resection and a 4-year follow-up or in case 2 with total resection and a 3-month follow-up.

The use of adjuvant therapy is still controversial, especially in incompletely resected tumors. The value of radiotherapy has not been established [2, 4, 11, 18], although chemotherapy may be required in cases of progressive disease with anaplastic features. There are not many reports dealing with the side effects of these types of treatment in children under 2 years. Four of out of five second malignancies occurred in children younger than 2 years of age at diagnosis with a cumulative risk at 8 years of 18.9% (CI 0–70%) [3].

Considering the young age of most patients and the danger of side-effects, we conclude from the available literature and our own experience that only follow-up by imaging is justified in these partially resected DIGs [3, 11, 14]. In cases where the tumor cannot be completely removed in one step the child should be allowed to recover and a second operation should be considered, as in our first case. In Fig. 4 we show a therapeutic plan for the management of a desmoplastic infantile ganglioglioma.

There may be a need for adjuvant chemotherapy in cases of deep seated tumors with aggressive behavior. However, because of the small number of patients, our conclusions should be interpreted with caution and further investigations are needed. We should think about a multicentric interdisciplinary study group that could collect data and give advice about the therapy for these rare tumors.

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