Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients

Josef Zentner, Helmut K Wolf, Burkhard Ostertun, Andreas Hufnagel, Manuel G Campos, Laszlo Solymosi, Johannes Schramm

Abstract
Clinical, radiological, and histopathological features of 51 surgically treated gangliogliomas were evaluated retrospectively. The most common presenting symptoms were epileptic seizures (47 patients (92%)). Focal neurological deficits occurred in 8% of the patients. The duration of symptoms at the time of operation ranged from three months to 45 years, mean 11 years. The temporal lobe was affected in 43 patients (84%), the frontal lobe in five patients (10%), and the occipital lobe in one patient (2%). Two of the tumours (4%) were localised infratentorially. On MRI, solid tumour parts usually showed a pronounced signal increase on proton density images and a less pronounced signal increase on T2 weighted images, whereas solid components were mainly isointense on T1 weighted images. Contrast enhancement was noted in 16 of 36 patients (44%). Cystic tumour parts were found in 23 of 40 patients (57%), all characterised by signal increase on T2 weighted images and decreased T1 signals. Signal deviation of cystic tumour parts on proton density images was variable. Computed tomography was performed in 17 patients and showed hypodense lesions in 10 (59%), and calcifications in seven (41%) cases. Surgery included complete tumour removal in 44 patients (86%) and partial resection in seven (14%). In six patients (12%), there were transient postoperative complications. One patient (2%) died postoperatively due to pulmonary embolism. Histopathological examination of the surgical specimens showed low grade gangliogliomas in 49 cases (96%) and anaplastic gangliogliomas in two (4%). Control MRI of 31 patients with a mean follow up period of 16 months was uneventful in all but one case of an anaplastic ganglioglioma. In all patients in whom the ganglioglioma was associated with medically intractable seizures the operation resulted in complete relief of seizures or a noticeable improvement of the epilepsy.

Keywords: Ganglioglioma; magnetic resonance imaging; computerised tomography; temporal lobe epilepsy.
Table 1 Signs and symptoms in 51 patients with gangliogliomas

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>47</td>
<td>(92)</td>
</tr>
<tr>
<td>Cranial nerve deficit</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Tetraparesis</td>
<td>2</td>
<td>(4)</td>
</tr>
<tr>
<td>Intracranial pressure (ICP)</td>
<td>2</td>
<td>(4)</td>
</tr>
</tbody>
</table>

Table 2 CT findings in 17 gangliogliomas. Frequency of hypodense (cystic), enhancing and calcified tumour components is shown. In one case, the tumour was not visible on contrast enhanced CT.

<table>
<thead>
<tr>
<th>CT pattern</th>
<th>Hypodense</th>
<th>Enhancing</th>
<th>Calcified</th>
<th>Patient No</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>6</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>1</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

Results

CLINICAL FINDINGS
There were 29 male and 22 female patients. Ages ranged from 2 to 50 (mean 25) years. Forty-seven patients (92%) were diagnosed with an epileptic seizure disorder that was pharmacoresistant in 40 cases (78%). The predominant seizure pattern was that of complex partial seizures. In three of the epileptic patients, the psychomotor development was noticeably retarded. Focal neurological deficits were found in four cases (8%). Two patients (4%) presented with signs of increased intracranial pressure (table 1). At the time of operation the duration of symptoms ranged from three months to 45 (mean 11) years. In patients treated for epilepsy, the mean duration of symptoms was 13 years as opposed to three years in patients operated on without chronic pharmacoresistant seizure disorders.

NEURORADIOLOGICAL FINDINGS
The tumours were located in the temporal lobe in 43 cases (84%), in the frontal lobe in five cases (10%), in the occipital lobe in one case (2%), and infratentorially with involvement of the pons and medulla oblongata in two cases (4%).

Native CT showed a hypodense lesion in 10 of 17 patients (59%). Calcifications were detected in seven cases (41%; fig 1). Lesion enhancement was present in five of 14 (36%) scans performed with contrast. The pattern of enhancement was inhomogeneous in two and homogeneous in three cases. The tumour was invisible on native CT in two cases (12%) and on contrast enhanced CT in one case (7%) (table 2).

Gangliogliomas appeared on MRI as entirely solid (n = 17; 43%), completely cystic (n = 2; 5%), or lesions with both solid and cystic parts (n = 21; 52%). Solid tumour parts were identified in 38 of 40 patients (95%). Only 36 patients were, however, examined with gadolinium. Of these, 10 contained one homogeneously enhancing solid component only (fig 2). The remaining six tumours were each composed of two different solid areas one of which was enhancing and the other non-enhancing. We evaluated the signal behaviour of these solid components separately so that a total of 44 solid tumour areas (38 plus six) were studied (table 3). The characteristic signal pattern of these 44 solid parts was a moderate or pronounced...
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Figure 2  MRI of an 18-year-old male patient with a ganglioglioma (WHO grade I) of the left supramarginal gyrus. T2 weighted axial (left) and contrast enhanced T1 weighted coronal images (right) are shown. The tumour enhances homogeneously. There is no evidence of cystic parts.

Figure 3  MRI of a 21-year-old patient with a ganglioglioma (WHO grade I) of the left uncus. Proton density weighted image (A) and T2 weighted image (B) show a homogeneous signal increase. T1 weighted image (C) shows decreased signal. Contrast enhanced T1 weighted image (D) shows an inhomogeneous signal increase of the solid tumour part, whereas the medially localised cystic component does not enhance.

Hyperintensity on proton density weighted images, whereas on T2 weighted images 14 of the 44 (32%) solid parts were isointense or even hypointense. On T1 weighted non-enhanced images, solid components were typically isointense. Cystic tumour components were found in 23 patients (57%). They were characterised by hypointensity on T1, strong hyperintensity on T2, and variable signal deviations on proton density weighted images (table 3; fig 3).

Surgical treatment and complications
Surgical treatment included complete tumour removal in 44 patients (86%) and partial resection in seven (14%). Of the 34 patients with temporal lobe gangliogliomas treated for medically intractable epilepsy, anterior temporal lobectomy including hippocampectomy was performed in 31 cases, and extended lesionectomy without hippocampectomy in three cases. In all six patients with gangliogliomas of the frontal or occipital lobe extended lesionectomy was performed.

Table 3  MRI findings in 40 gangliogliomas

<table>
<thead>
<tr>
<th>Tumour component</th>
<th>Signal deviation</th>
<th>Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spin echo sequence</td>
<td>No</td>
</tr>
<tr>
<td>Solid</td>
<td>T1</td>
<td>9</td>
</tr>
<tr>
<td>n = 44</td>
<td>PD</td>
<td>1</td>
</tr>
<tr>
<td>Cystic</td>
<td>T1</td>
<td>13</td>
</tr>
<tr>
<td>n = 23</td>
<td>PD</td>
<td>2</td>
</tr>
</tbody>
</table>

The solid tumour components were divided into enhancing and non-enhancing parts. Thus 44 solid tumour components were evaluated. Contrast enhancement was seen in 16 of 44 solid tumour components, whereas 28 did not enhance.

PD = proton density.
Arrows reflect increased [↑] or decreased [↓] signal. Circle diameters reflect degree of enhancement.
ganglioglioma (WHO grade I). The lesion consists of a mixture of disfigured ganglion cells and astrocytes. The ganglion cells are characterised by prominent nuclei and Nissl substance and lack of a uniform orientation (haematoxylin-eosin mixture originally ×240).

according to the results of presurgical epileptiological evaluation.

Intraoperatively, solid and cystic tumour components were easily recognised. The solid tumour parts were usually of a yellowish or brownish colour, often of firm consistency, and they were well demarcated from adjacent gyri and sulci. Cystic tumour parts were often seen between the solid components. Well differentiated tumours could be easily separated from surrounding structures such as the Sylvian fissure and the brain stem.

One patient (2%) died two weeks after operation due to massive pulmonary embolism. Transient morbidity was encountered in six patients (12%). These complications included third nerve paresis in two cases, wound infection requiring removal of the bone flap in one case, and deep vein thrombosis in another case. Two patients had mild temporary peripheral nerve deficits probably due to inadequate positioning on the operation table. All these complications eventually resolved completely.

HISTOPATHOLOGICAL FINDINGS
Histologically, the gangliogliomas were characterised by an intimate mixture of neoplastic astrocytes and atypical ganglion cells (fig 4). Nissl stains and immunohistochemical stains for neuronal (synaptophysin, NFP, NSE) and astrocytic (GFAP) markers were useful in highlighting the neuronal and glial cell populations and provided a valuable aid for the diagnosis of small and fragmented tumour samples. Ganglion cells were identified as such by the demonstration of Nissl substance and large nucleoli. According to the WHO classification, we found WHO grade I tumours in 44 patients (86%). Based on a high cellularity and cellular and nuclear pleomorphism of the glial component, five tumours (10%) were classified as WHO grade II lesions. Two gangliogliomas (4%) contained areas of pronounced hypercellularity, vascular proliferation, necrosis, and many mitotic figures in the astrocytic component and thus fulfilled the criteria of anaplasia. These tumours were characterised as WHO grade III lesions. In many patients, the ganglioglioma was associated with one or more glioneural hamartias, which are microscopic malformed lesions composed of glial elements and ganglion cells. One of the two cases of anaplastic gangliogliomas has recently been described elsewhere.17

FOLLOW UP EXAMINATION
Clinical data on follow up examinations were available in 40 patients, all of whom had presented with pharmaco-resistant epilepsy. Of these, 32 patients (80%) were seizure free and eight (20%) had a reduction in seizure frequency of more than 75%.

Postoperative MRI controls were obtained from 31 patients. There was no evidence of any recurrent or progressive tumour apart from one case. In this patient an anaplastic ganglioglioma of the mesial temporal lobe had been only incompletely removed. Magnetic resonance imaging performed six months after operation showed a small residual tumour along the Sylvian fissure. Twelve months after operation, MRI showed several zones of signal increases on T2 weighted images in the fourth ventricle and the cervical and thoracic subarachnoid space. Thus drop metastases along the CSF pathways were suspected. A cytological examination of CSF, however, did not show tumour cells. The residual tumour along the Sylvian fissure was unchanged with no clear evidence of tumour progression.

Neurological examination at this time showed no abnormalities. The other patient with an
anaplastic ganglioglioma died shortly after operation due to pulmonary embolism.

Discussion

Gangliogliomas are tumours of the CNS that are composed of atypical ganglion cells and astrocytes. Zülch found gangliogliomas in 0-4% and Cushing in 0-3% of a comprehensive series of brain tumours. According to recent studies, gangliogliomas account for 0-4% to 7-6% of paediatric CNS neoplasms and up to 1-3% of those in adults. The high ratio of gangliogliomas among brain tumours at our institution (5-2%) reflects the high incidence of this tumour in patients with epilepsy.19-21 The temporal lobe is the most common location of gangliogliomas.\(^5\) 5 6 22 23 Also, gangliogliomas may be found at virtually any location of the CNS such as the spinal cord,\(^24\) 27 brain stem,\(^28\) 29 third and fourth ventricle,\(^30\) cerebellum,\(^31\) 32 pineal region,\(^33\) 34 thalamus,\(^3\) and optic nerve.\(^35\) 36

Most patients present with long histories of seizures, whereas focal neurological deficits or increased intracranial pressure are unusual. In our series, epilepsy was found in 47 of 51 patients (92%). This is in agreement with previous reports in which seizures were the presenting symptom in 62 to 100% of patients with hemispheric tumours.\(^1 \) 4 5 11 13 36 Focal neurological deficits, as present in four of our patients (8%), have mainly been found in patients with parietal tumours or tumours in locations such as the thalamus, brain stem, or spinal cord.\(^1\) The age at presentation ranged between 2 and 50 (mean 25) years in our series, which is similar to other reports.\(^4\) 5 13

There was no sex preponderance in any of the reported series, including our own.

Our CT findings are similar to other series. The tumours were hypodense in 59%. Calcifications were present in 41% and there was contrast enhancement in 36%. Hypodense lesions on CT were reported in the literature in 40 to 100%, calcifications in 20 to 50%, and contrast enhancement in 16 to 80% of gangliogliomas.\(^1 \) 4 5 10 11 36 The fact that the tumour was invisible on native CT in two of our patients and on contrast enhanced CT in one case highlights the importance of MRI for the diagnosis of gangliogliomas.

Magnetic resonance imaging has proved to be more sensitive in identifying gangliogliomas than CT. In agreement with previous reports,\(^10\) 11 57% of the tumours had cystic components, which were hypointense on T1 weighted images and hyperintense on T2 weighted images. Forty three per cent of the tumours appeared only as solid lesions with typically pronounced signal increase on proton density weighted images and less pronounced hyperintensity on T2 weighted images. Most remarkably, there was usually isointensity on T1 weighted images. The pattern of contrast enhancement in MRI studies of gangliogliomas has not been reported in detail in previous studies. Gadolinium enhancement was present in 16 of 36 patients (44%) in our series. Magnetic resonance imaging was performed in eight patients in the series of Haddad et al with contrast enhancement in one patient (12%).\(^11\) Hypointense lesions on T1 and hyperintense lesions on T2 weighted images were also found in two spinal gangliogliomas.\(^37\) Tumour cysts may show a higher signal than CSF on T2 weighted images. Irregular margins and associated soft tissue components help to distinguish the tumour cysts from simple cysts. This corresponds with the intraoperative finding that cystic tumour parts may consist of a gelatinous mass.\(^3\) Moreover, MRI is a valuable aid in defining the location and border of a tumour in different planes, which is indispensable for the planning of complete tumour removal. Tampieri et al,\(^20\) however, found two patients with gangliogliomas, in whom MRI was normal. In our series there was a single case in which the ganglioglioma was not detected by MRI, probably due to the technical limitations of a first generation MRI scanner.

The extent of resection is thought to be the main prognostic factor in the treatment of gangliogliomas.\(^1 \) 11 The present results with a complete seizure relief in 80% and a significant improvement (> 75% reduction in seizure frequency) in the remaining 20% of the patients compare favourably with most previous reports on smaller series in which relief of seizures after operation was found in 50-90% of the patients.\(^5 \) 9 11 13 In accordance with Haddad et al,\(^11\) all patients with total resection were tumour free at the last follow up.

For most gangliogliomas, radiation therapy seems to be of no benefit.\(^5\) 11 None of our patients received postoperative irradiation treatment. Garrido et al found no difference in outcome with or without radiation therapy in four cases. Most authors recommend that radiation therapy should be reserved only for those patients with tumour progression.\(^1 \) 3 13 15 Whether anaplastic gangliogliomas will benefit from radiation therapy or chemotherapy has not been studied. In one case of anaplastic ganglioglioma in our series, MRI indicated spinal drop metastases 12 months after surgery, which suggests that postoperative radiation therapy might be useful in anaplastic gangliogliomas (WHO grade III). Similarly, the relevance of increased cellularity and cellular and nuclear anaplasia (WHO grade II lesions) remains uncertain at the present time and is awaiting long term follow up.

The origin of gangliogliomas remains obscure. Some findings support the hypothesis that gangliogliomas represent developmental lesions. These include histopathological evidence of disordered neuronal migration and a long clinical history in many patients. A single case of a congenital ganglioglioma of the occipital lobe presenting with quadriplegia has been reported.\(^3\) 6

In conclusion, gangliogliomas are usually benign tumours composed of neuronal and glial elements. The temporal lobes are the preferred site. Clinically, gangliogliomas are
typically associated with chronic pharmacoresistant epileptic seizure disorders in children or younger adults. Neuropathologically, there is no single pathognomonic finding. In the appropriate clinical setting, a ganglioglioma should be strongly considered in the presence of a tumour like lesion with both solid and cystic components on MRI. The presence of calcifications, which are more readily detected by CT than MRI, provides further support for the tentative diagnosis of a ganglioglioma. Complete tumour removal seems to be the treatment of choice. In patients with medically intractable epilepsy, surrounding brain areas that are considered to be epileptogenic as determined by extensive presurgical evaluation should also be excised. Although most gangliogliomas appear histopathologically benign and run a clinical benign course, long term follow up of additional cases is necessary for a clear definition of the biological behaviour of these lesions.

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