Glioneuronal Tumors and Epilepsy: Clinico-Diagnostic Features and Surgical Strategies

Alessandro Consales, Paolo Nozza, Maria Luisa Zoli, Giovanni Morana and Armando Cama

Abstract Glioneuronal tumors (GNTs) are a set of tumors of the Central Nervous System (CNS) composed entirely or partially of cells with neuronal differentiation. The description applies to several tumors referred to in the Classification of the World Health Organization (WHO) as neuronal and mixed neuronal-glial tumors. Some of them arise tipically in the cerebral cortex and represent a common cause of drug-resistant focal epilepsies in children and young adults. Three groups of tumors are of considerable relevance: ganglion cell tumors (GCTs), ganglioglioma (GG) being the typical example, dysembryoplastic neuroepithelial tumors (DNTs) and neurocytic tumors, namely extraventricular neurocytoma. GNTs commonly arise from a cortex housing developmental malformations, that are able to provoke seizures, such as focal cortical dysplasia (FCD) and, less frequently, hyppocampal sclerosis (HS). Management of patients with GNTs includes dealing with both tumor and epilepsy. From the neuro-oncological point of view, consistently with the long clinical history, these tumors are generally considered as low-grade gliomas (LGGs). They correspond to grades I or II of the WHO classification and their therapy relies mainly on surgery. However, tumor progression or transformation into higher grade tumors may occur.

From the neurological point of view, it is noteworthy that seizures are likely to respond very well to surgical treatment. Despite the favorable seizure outcome, the best surgical strategy has not been fully established yet. Indeed, while some authors regard tumor resection (the so-called lesionectomy) alone as sufficient for complete

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seizure control, other investigators also recommend the additional resection of peritumoral epileptogenic zones to maximize the seizure outcome.

Anyway, surgical treatment should be planned on the basis of anatomo-electroclinical correlation defining the epileptogenic zone to be resected.

To conclude, in patients with GNTs-related epilepsies, surgery should be proposed in order to obtain complete seizure control with freedom from antiepileptic drugs (AEDs), and to prevent tumor growth and risk of malignant transformation.

List of abbreviations

ADC	Apparent Diffusion Coefficient
AED(s)	Antiepileptic Drug(s)
BBB	Blood Brain Barrier
CNS	Central Nervous System
Cho	Choline
CT	Computed Tomography
DWI	Diffusion Weighted Imaging
DNT(s)	Dysembryoplastic Neuroepithelial Tumor
ECoG	Electrocorticography
EEG	Electroencephalography
FCD	Focal Cortical Dysplasia
GCT(s)	Ganglion Cell Tumor(s)
GG(s)	Gangliоglioma(s)
GNT(s)	Glioneuronal Tumor(s)
H&E	Hematoxylin & Eosin
HS	Hyppocampal sclerosis
LGG(s)	Low-grade glioma(s)
mI	myo-inositol
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-acetyl aspartate
PWI	Perfusion Weighted Imaging
rCBV	relative Cerebral Blood Volume
VFD(s)	Visual Field Defect(s)
WHO	World Health Organization

Glioneuronal tumors (GNTs) are a set of tumors of the Central Nervous System (CNS) composed entirely or partially of cells with neuronal differentiation, diagnosed mainly by means of histochemical and immunohistochemical stainings and, more rarely, by electron microscopy. The description applies to several tumors referred to in the Classification of the World Health Organization (WHO) as neuronal and mixed neuronal-glial tumors (Daumas-Duport et al. 1988; Louis et al. 2007a; Allende and Prayson 2009). Some of them arise tipically in the cerebral cortex and represent a common cause of drug-resistant focal epilepsies in children and young adults (Aronica et al. 2001; Benifla et al. 2006; Cataltepe et al. 2005; Consales

et al. 2013; Clusmann et al. 2004; Daumas-Duport et al. 1988; Giulioni et al. 2005; Morris et al. 1998; Nolan et al. 2004). Three groups of tumors are of considerable relevance: ganglion cell tumors (GCTs), gangliоglioma (GG) being the typical example, dysembryoplastic neuroepithelial tumors (DNTs) and neurocytic tumors, namely extraventricular neurocytoma. However, this classification scheme is rather arbitrary and provisional. Tumors with composite features, such as GG and DNT may occur and new entities will probably be described. On the other hand, it could sometimes be difficult to distinguish a tumor from a malformation of cortical development (Prayson and Napekoski 2012). From a more general point of view, it should be kept in mind that also tumors not included in the chapter of neuronal and neuronal glial tumors, should be included in the more general classification of 'long-term epilepsy-associated tumors'. Some of them, such as the pleomorphic xanthoastrocytoma, may show neuronal differentiation, while some others, such as the pilocytic astrocytoma or 'isomorphic astrocytoma', are astrocytic tumors. All of them make clear however that, to induce long-term epilepsy, a tumor need not be composed of neuronal cells (Blümcke et al. 2004).

Furthermore, GNTs commonly arise from a cortex housing developmental malformations, that are able to provoke seizures, such as focal cortical dysplasia (FCD) (40–80% of cases) and, less frequently (up to 25% of cases), hyppocampal sclerosis (HS) (Aronica et al. 2001; Bilginer et al. 2009; Blümcke and Wiestler 2002; Cataltepe et al. 2005; Chang et al. 2010; Minkin et al. 2008; Nolan et al. 2004; Prayson et al. 2010; Sharma et al. 2009).

Therefore, management of these cases includes dealing with both tumor and epilepsy.

From the neuro-oncological point of view, consistently with the long clinical history, these tumors are generally considered as low-grade gliomas (LGGs). They correspond to grades I or II of the WHO classification and their therapy relies mainly on surgery (Becker et al. 2007; Daumas-Duport et al. 2007). However, tumor progression or transformation into higher grade tumors may occur (Aronica et al. 2001; Nolan et al. 2004; Hall et al. 1986; Hammond et al. 2000; Kim et al. 2003; Luyken et al. 2004).

From the neurological point of view, it is noteworthy that seizures are likely to respond very well to surgical treatment (Aronica et al. 2001; Cataltepe et al. 2005; Luyken et al. 2003; Clusmann et al. 2002; Clusmann et al. 2004).

Despite the favorable seizure outcome, the best surgical strategy has not been fully established yet. Indeed, while some authors regard tumor resection (the so-called *lesionectomy*) alone as sufficient for complete seizure control (Giulioni et al. 2005; Bourgeois et al. 2006; Iannelli et al. 2000; Montes et al. 1995), others recommend the resection of peritumoral epileptogenic zones (Aronica et al. 2001; Clusmann et al. 2004; Morris et al. 1998; Cossu et al. 2008; Kim et al. 2008; Luyken et al. 2003).

The aim of this chapter is to elaborate on the current concepts concerning the diagnosis and surgical management of patients with medically intractable focal epilepsy related to GNTs.

Epidemiology and Type of Tumors

GNTs account for 0.4–1.3 % of all brain tumors (Becker et al. 2007; Daumas-Duport et al. 2007) and are an increasingly recognized cause of epilepsy in children and young adults (Aronica et al. 2001; Benifla et al. 2006; Cataltepe et al. 2005; Consales et al. 2013; Clusmann et al. 2004; Daumas-Duport et al. 1988; Giulioni et al. 2005; Morris et al. 1998; Nolan et al. 2004).

Their incidence in the pediatric population is about 8 %, accounting for up to 30 % of long-standing medically intractable epilepsies (Aronica et al. 2001; Daumas-Duport et al. 1988; Johnson et al. 1997; Obeid et al. 2009; Zaghloul and Schramm 2011). Among telencephalic GNTs (box 1), seizures are reported in up to 100 % of DNTs and in 80–90 % of GGs (Chang et al. 2008; Englot et al. 2011; van Breemen et al. 2007; Zaghloul and Schramm 2011).

Box 1

Neuronal and mixed neuronal-glial tumors (WHO Classification) (Louis et al. 2007b)

(in bold are tumors relevant for epilepsy surgeons)

Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	WHO Grade I
Desmoplastic infantile astrocytoma/ganglioglioma	WHO Grade I
Dysembryoplastic neuroepithelial tumor	**WHO Grade I**
Gangliocytoma	**WHO Grade I**
Ganglioglioma	**WHO Grade I**
Anaplastic ganglioglioma	WHO Grade III
Central neurocytoma	WHO Grade II
Extraventricular neurocytoma	**WHO Grade II**
Cerebellar liponeurocytoma	WHO Grade I
Papillary glioneuronal tumor	WHO Grade I
Rosette-forming glioneuronal tumor of the fourth ventricle	WHO Grade I
Paraganglioma	WHO Grade I

Mechanisms of Epileptogenesis Associated with GNTs

The pathophysiological mechanisms of epileptogenesis associated with brain tumors are not well understood. Several pathogenetic factors have been advocated to explain the tumor-related epileptogenesis.

Schematically, three types of mechanisms have been hypothesized, namely: (a) intrinsic to the lesion itself, including the expression of various ion channels and the relative proportion of different cell types within the tumor (Aronica et al. 2001;

Ventureyra et al. 1986; Rossi et al. 1999); (b) intrinsic to the tumor location, including peritumoral amino acid disturbances, local metabolic imbalance, cerebral edema, pH abnormalities, neuropil changes, neuronal/glial enzyme changes, altered protein expression and immunological activity (Beaumont and Whittle 2000); (c) unique to the patient harboring the disease (Gaggero et al. 2009; Wetjen et al. 2004).

There is significant evidence in the literature supporting the view that GNTs have intrinsic epileptogenic activities due to their neuronal and glial components (Aronica et al. 2001; Blümcke and Wiestler 2002; Daumas-Duport et al. 1988; Prayson et al. 1995; Prayson et al. 1996; Prayson 1999; Zentner et al. 1994). The neurochemical profile of GNTs shows some similarities in expression of various enzymes and receptors to that of neocortical neurons (Aronica et al. 2001; Aronica et al. 2007; de Groot et al. 2010; Lee et al. 2006). Moreover, the relatively low incidence of HS associated with temporal GNTs suggests that these tumors may be the primary source of epilepsy (Beaumont and Whittle 2000; Blümcke and Wiestler 2002).

The association between GNTs and other epileptogenic lesions (as FCD) has been frequently reported, however the specific role of each of them in determining epilepsy is not well understood (Beaumont and Whittle 2000; Louis et al. 2007b; Prayson et al. 2010). This implicates that simple tumor resection in patients affected also by FCD may determine unsatisfactory seizure outcome.

Finally, it is important to consider that the epileptogenic focus is not located within the tumor in about 30–40 % of patients. The presence of a secondary epileptogenic focus must be postulated, particularly in patients affected by temporal tumors (van Breemen et al. 2007).

Electroclinical Features

Focal epilepsy represents the most common clinical feature. Seizures are often the only symptom. Neurological deficits are quite rare, probably because of the slow growth of GNTs. Epilepsy can present at any age, even if most cases are diagnosed during the adolescence. Seizure type depends on tumor location. Status epilepticus is rare. There does not seem to be differences ascribable to tumor type (DNT, GG, or rarer tumors). The response of GNTs-related epilepsy to antiepileptic drugs (AEDs) is often discouraging, with frequent development of drug-resistance. Short duration of epilepsy, partial seizures and lack of secondary generalization are the most important clinical prognostic factors for a successful seizure outcome. There are two differences between children and young adults concerning the characteristics of GNTs-related epilepsy: a) aura is diagnosed more frequently in young adults; b) mean age at seizure onset is lower in children. This can be explained, respectively, by the limited capability of children to describe their symptoms and their lower seizure threshold (Ozlen et al. 2010).

In the non-invasive diagnostic work-up of patients, long-term neurophysiological monitoring, such as Video-EEG, is very useful in recording seizures and identifying the epileptogenic zone.

Concerning EEG features, interictal data usually consist of spikes and/or sharp waves, sometimes intermixed with slow activities. There is also the possibility of

a normal EEG. The abnormal features are usually lateralized to the tumor side. This does not guarantee good seizure outcome after tumor resection. In addition, it should be stressed that satisfactory seizure outcome can be achieved after tumor surgery even in patients whose EEG epileptiform activities are not localized to the tumor site (Morris et al. 1998).

When it is not possible to determine the lateralization of seizure focus by means on non-invasive diagnostic investigations, intracranial EEG (Stereo-EEG, depth electrodes, ECoG) may provide useful information. However, intracranial recordings are mainly aimed at mapping eloquent cortex when tumor resection in critical areas is planned. Thus, little is presently known, for example, about ECoG spike discharge patterns in patients with GNTs (Ferrier et al. 2006).

On the other hand, it is commonly acknowledged that patients with GNTs and FCDs may have similar invasive EEG patterns (Chassoux et al. 2000; Chassoux and Daumas-Duport 2013).

Ganglion Cell Tumors (GCTs)

GG and gangliocytoma are neuroepithelial tumors composed of ganglion cells (gangliocytoma) or both ganglion and glial cells (GG). The distinction seems slightly artificial and seldom acquires a deep, practical significance. Thus, these tumors can be lumped together under the designation 'GCTs'.

They are the most common tumors determining drug-resistant epilepsy and account for over 40% of all epileptogenic tumors in most surgical series (Lawson and Duchowny 2004).

GCTs of the cerebral cortex mainly occur in the temporal lobe and, secondarily, in the frontal lobe (Casazza et al. 1989; Otsubo et al. 1990–1991). They can occur throughout the neuraxis (Becker et al. 2007).

Neuroimaging characteristics are variable (Fig. 1a, b, c, d and Fig. 2a, b) as these tumors may present as a mixed lesion (solid and cystic), as a purely solid mass or, less commonly, as a cyst (Zentner et al. 1994; Castillo et al. 1990; Raybaud et al. 2006). Classically, GG has been described as a cystic mass with a mural nodule in approximately 40% of cases. On non contrast CT, most GGs are hypodense to gray matter, but some can have mixed or high density. Calcifications are relatively common and are reported in about 35–50% of cases (Castillo 1998). Scalloping of the calvarium may be seen. Sometimes this neoplasm may be undetectable on CT. On MRI, the signal behavior is variable as well, with a spectrum of signal intensity depending on the neuropathological features of the different components. Solid portions are iso- to hypointense on T1-weighted images, with a variable degree of hyperintensity on T2-weighted images.

Cystic components, hypointense on T1- and hyperintense on T2-weighted images, may or may not show wall enhancement following gadolinium injection (Zhang et al. 2008). Enhancement of the solid portion is highly variable, ranging from no enhancement to intense homogeneity; grossly half of tumors display at least some degree of enhancement. There is usually little associated mass effect or surrounding

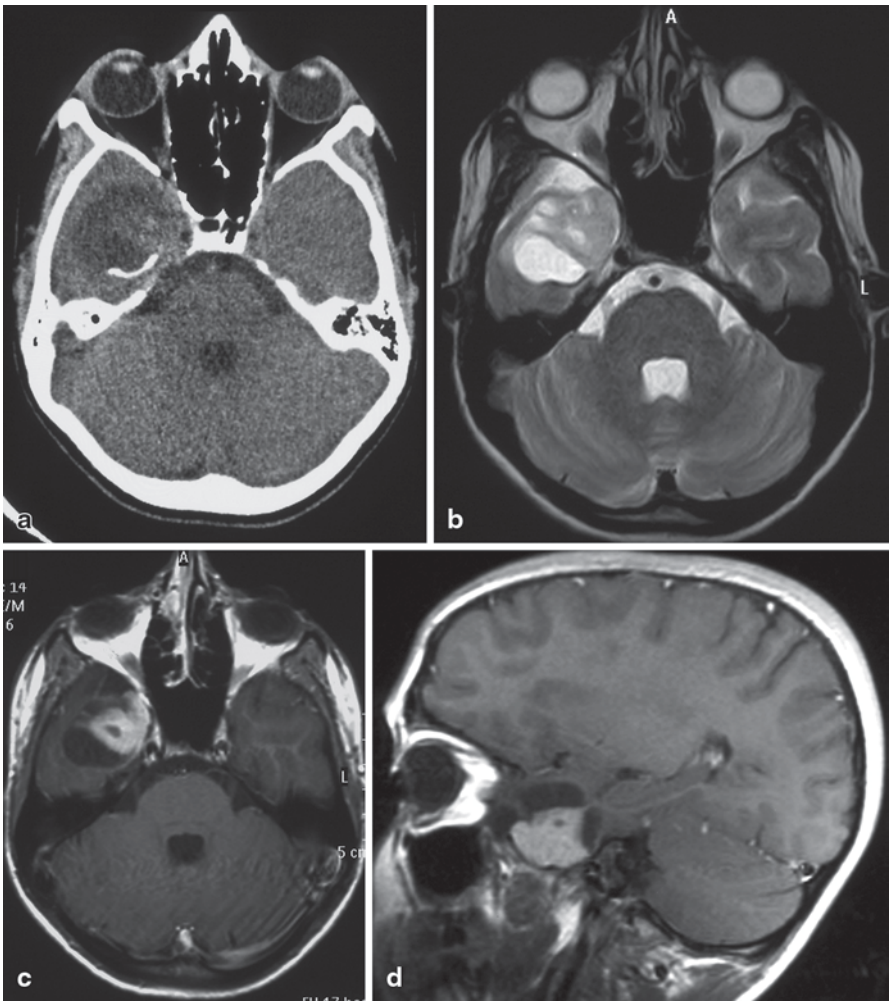

Fig. 1 GG in a 10-year-old girl.**a** Axial CT scan. **b** Axial T2-weighted image. **c** Axial Gd-enhanced T1-weighted image. **d** Sagittal Gd-enhanced T1-weighted image. CT shows an heterogeneous, prevailingly hypodense, mass lesion in the right temporal pole with gross, shell-like calcifications (**a**). The tumor has a cortical location and cystic and solid appearance (**b**). The solid component is mildly hyperintense on T2-weighted image (**b**) with marked enhancement following gadolinium injection (**c**, **d**)

vasogenic edema. Intratumoral hemorrhage is uncommon. Leptomeningeal or ependymal seeding may rarely occur (Adachi and Yagishita 2008).

Diffusion weighted imaging (DWI) shows increased diffusivity (high signal on ADC maps), whereas perfusion weighted imaging (PWI) demonstrates lower rCBV values compared to normal parenchyma. On magnetic resonance spectroscopy (MRS), most GGs display the features of a LGG, with decreased N-acetyl aspartate (NAA) and mildly elevated Choline (Cho).

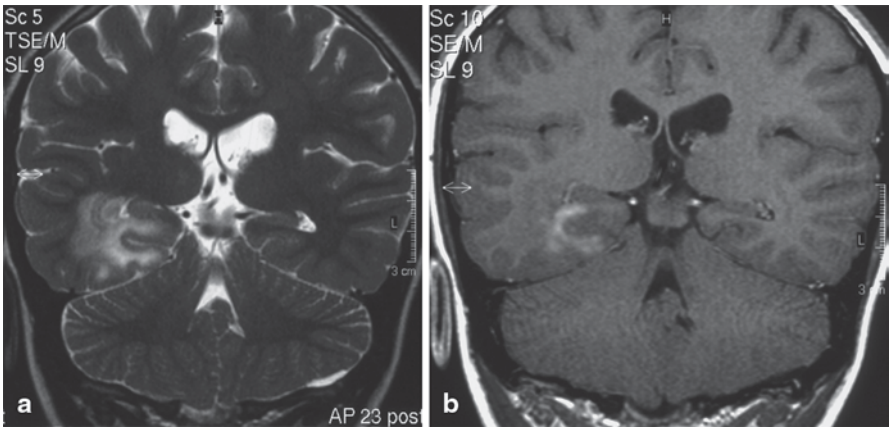

Fig. 2 GG in a 10-year-old boy.**a** Coronal T2-weighted image. **b** Coronal Gd-enhanced T1-weighted image. Lesion involving the right mesial temporal structures, with mild swelling of the parahippocampal region, hyperintense on T2-weighted image (**a**). Following gadolinium injection the lesion enhances. No cystic components are present

From the neuropathological point of view, the key feature is the presence of neoplastic ganglion cells. They differ from normal ganglion cells—large cells with vesicular nuclei, central and prominent nucleoli, and abundant cytoplasm—because of abnormalities of size, shape, cell processes, irregular accumulation of Nissl substance and cytoplasmic vacuolization. Cellular gigantism and bi- or multinucleation are a common finding (Fig. 3a). These cells do not achieve any degree of architectural uniformity.

Neurofibrillary tangles, granulo-vacuolar degeneration and basic cellular neuronal lesions typical of neurodegenerative diseases may be observed.

Neoplastic glial cells, whose presence is a requisite for the diagnosis of GG, have a variable morphology, which can make the tumor resemble a pilocytic astrocytoma,

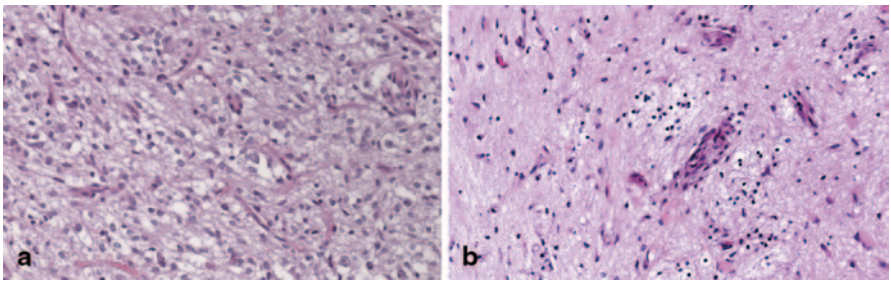

Fig. 3 GG**a** H&E, 200x. Gangliogliomas are typically non-infiltrating tumors; several multinucleated cells, which immunohistochemistry can prove to be neurons, are seen. **b** H&E. Lymphocytes are common

a diffusely infiltrating astrocytoma or even an oligodendroglial tumor. Melanotic cells may be found (Soffer et al. 1992).

The stroma is rich in reticular fibers, which encircle not only vessels, as in normal brain, but also neoplastic cells.

Vascular proliferation may be seen. The presence of hemosiderin deposits is an evidence of prior hemorrhage and, like contrast enhancement, is related to an impairment of the blood brain barrier (BBB). Intratumoral BBB dysfunction in concert with subsequent accumulation of albumin by neoplastic glial cells may represent an epileptogenic mechanism underlying tumor-associated long-term epilepsy (Schmitz et al. 2013).

Rosenthal fibers, basic astrocytic lesions, typical of fibrillary gliosis, and eosinophilic granular bodies are often observed. Lymphocytic infiltration is typical (Fig. 3b)

Necrosis is rare except in anaplastic cases.

It is interesting to note that temporal lobe GGs express CD34 glycoprotein, which apparently is not expressed in the frontal or parietal lobe tumors and it could be a marker of epileptogenic dysplasia (Kerkhof and Vecht 2013; Blümcke and Wiestler 2002).

GGs Grading

The third edition of the WHO Classification of CNS Tumors (Kleihues and Cavenee 2000) admitted the existence of atypical GGs, corresponding to grade II. Atypical tumors should have been distinguished from typical ones on the basis of cellularity, nuclear pleomorphism, microvascular proliferation, and proliferation index (>5%). Furthermore, necrosis and a proliferation index (>10%) should have been the hallmarks of anaplastic tumors. Unluckily, these criteria are unable to reliably predict the clinical behavior (Wolf et al. 1994; Luyken et al. 2004; Selvanathan et al. 2011). The fourth edition of the Classification includes no longer grade II (Louis et al. 2007b).

Although microscopic signs of atypia or anaplasia mostly occur in the glial component, they may occur in neuronal cells, too (Jay et al. 1994). Although anaplastic tumors typically appear *de novo*, one tenth of them is the result of the transformation of a GG. Anaplastic transformation is more common in pediatric cases and is associated with previous subtotal tumor resection and radiotherapy (Im et al. 2002).

Dysembryoplastic Neuroepithelial Tumor (DNT)

Although they may occur throughout the CNS, DNTs are cortical-based tumors, that typically affect children and young adults with long-standing pharmacoresistant epilepsy (Daumas-Duport et al. 1988, 2007).

DNTs of the cerebral cortex typically appear in the *isocortex* or in the *allocortex* of the temporal lobe; these tumors can arise in the frontal lobe and, sporadically, in the parietal and occipital lobes (Daumas-Duport et al. 1988; Thom et al. 2011).

Although there seems to be a relationship between DNTs and the development of the cerebral cortex, and cortical malformations may coexist alongside, from the neuro-oncologic point of view DNTs are considered as LGGs corresponding to grade I of the WHO Classification (Thom et al. 2011; Louis et al. 2007b).

Initially, the cells of the subpial granular layer were considered the source of this tumor(Daumas-Duport et al. 1988).

DNT coexistence with FCD (Daumas-Duport et al. 2007), neuronal heterotopia (Honavar et al. 1999), microdysgenesis (Rojiani et al. 1996) and neurofibromatosis type 1 (Lellouch-Tubiana et al. 1995) supports the hypothesis of a developmental origin.

DNTs show minimal or no mass effect and absence of peritumoral edema. On CT scan, they appear as a hypoattenuating lesion that may occasionally present areas of calcification and remodeling of the adjacent inner table of the skull. On MRI, the typical appearance consists of a well demarcated pseudocystic lesion, strongly hyperintense on T2- and hypointense on T1-weighted images, with variable FLAIR signal (hypo-isointense or hyperintense). DNTs may have a gyriform or a triangular-shaped pattern with the base pointing to the cortical surface. Hyperintense stripes on FLAIR images are visible both along the surface (bright rim) and on thin septa, resulting in a multicystic, bubbly appearance. Additional small cysts are often located in the vicinity, separated from the main mass.

Some lesions may show a more heterogeneous signal consistent with solid, cystic or semiliquid structures. Solid tissue is usually interspersed between the pseudocysts and it is often found in the adjacent subcortical white matter. Contrast enhancement is rare, variable, and often ring-like (Fig. 4a, b, c, d and Fig. 5a, b, c). Hemorrhage is also uncommon (Daumas-Duport et al. 1988; Daumas-Duport 1993; Ostertun et al. 1996; Campos et al. 2009). Diffusion and perfusion weighted images show respectively increased diffusivity and low rCBV values. The MRS pattern is nonspecific with increase in myo-inositol (mI) and slight reduction of NAA. Lactate and lipids are usually absent (Bulakbasi et al. 2007).

The neuropathological key feature is a microscopic structure, the *specific glioneuronal element*, which assumes the leading role in the *simple* forms, sharing the stage with the *glial nodules* in the *complex* forms. A highly controversial set of neuroepithelial tumors lacking the specific glioneuronal element has been classified as nonspecific or diffuse forms (Thom et al. 2011; Honavar et al. 1999; Bodi et al. 2012).

Simple and complex DNTs are generally circumscribed cystic lesions corresponding to type 1 of some neuroimaging classifications. The diffuse forms of the *neocortex* are quite nodular and sometimes calcific (type 2), the diffuse forms of the *allocortex* (mesial temporal lobe) tend to have dim outlines (type 3) (Chassoux and Daumas-Duport 2013; Chassoux et al. 2012).

The glioneuronal element is characterized by a mucoid matrix in which cells resembling oligodendrocytes align in a columnar fashion along bundles of axons and capillaries arrayed perpendicular to the pial surface. Mature neurons seem to float among the columns (Fig. 6a, b, c). Binucleate cells can be present; perineuronal satellitosis is not generally seen.

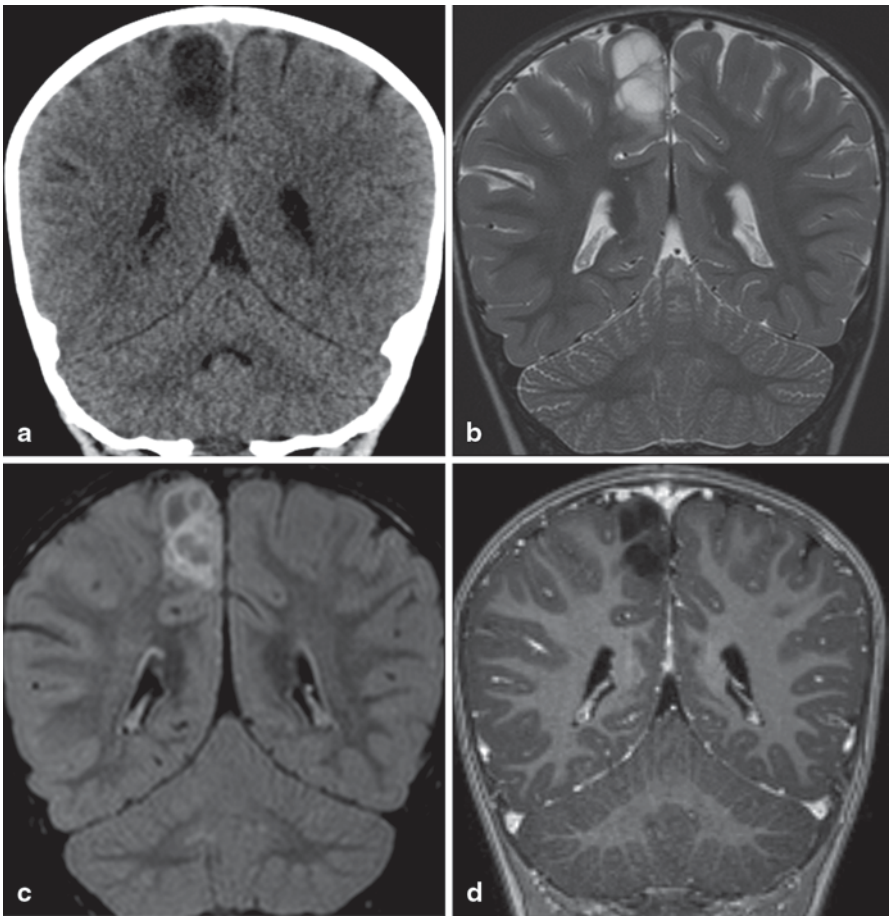

Fig. 4 DNT in a 6-year-old boy.**a** Coronal CT scan. **b** Coronal T2-weighted image. **c** Coronal FLAIR image. **d** Coronal Gd-enhanced T1-weighted image. Right paracentral lobule, cortical-subcortical, lesion whose density (**a**) and signal intensity on T2 (**b**) is cystlike. Corresponding FLAIR image (**c**) shows bright internal septa and lesion periphery producing a multicystic "bubbly" appearance. Following gadolinium administration enhancement is absent (**d**)

The glial nodules, which may contain neurons, are made up of astrocytes and oligodendrocytes, showing a variable degree of differentiation or pleomorphism. The nodules may resemble pilocytic astrocytoma or 'diffuse gliomas' (Fig. 6d).

Calcifications may be observed (Daumas-Duport et al. 1988; Thom et al. 2011); ossification is an exceptional finding (Thom et al. 2011).

These tumors have the capability both to cross the cortical sulci and to extend into the white matter and the leptomeninges (Thom et al. 2011; Zhang et al. 2013). White matter may show loss of myelin, gliosis and mycrocysts (Thom et al. 2011). HS, more commonly atypical (end-folium sclerosis) than classic, is common (Thom et al. 2011). Neurofibrillary tangles may be observed. The presence of intracellular pigments, such as iron or melanin, is quite common (Thom et al. 2011).

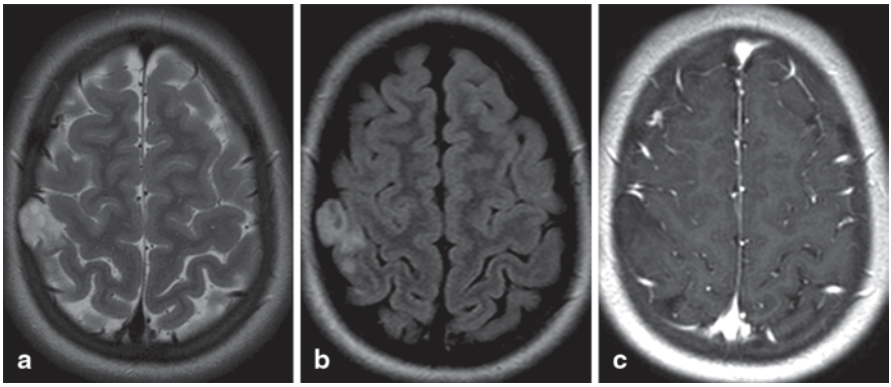

Fig. 5 DNT in a 9-year-old girl.**a** Axial T2-weighted image. **b** Axial FLAIR image. **c** Axial Gd-enhanced T1-weighted image.Superficially located tumor involving the right postcentral gyrus with remodeling of the adjacent calvarium (**a**). Two small internal pseudocysts are visibile on FLAIR image (**b**). There is no enhancement on post contrast T1-weighted image (**c**)

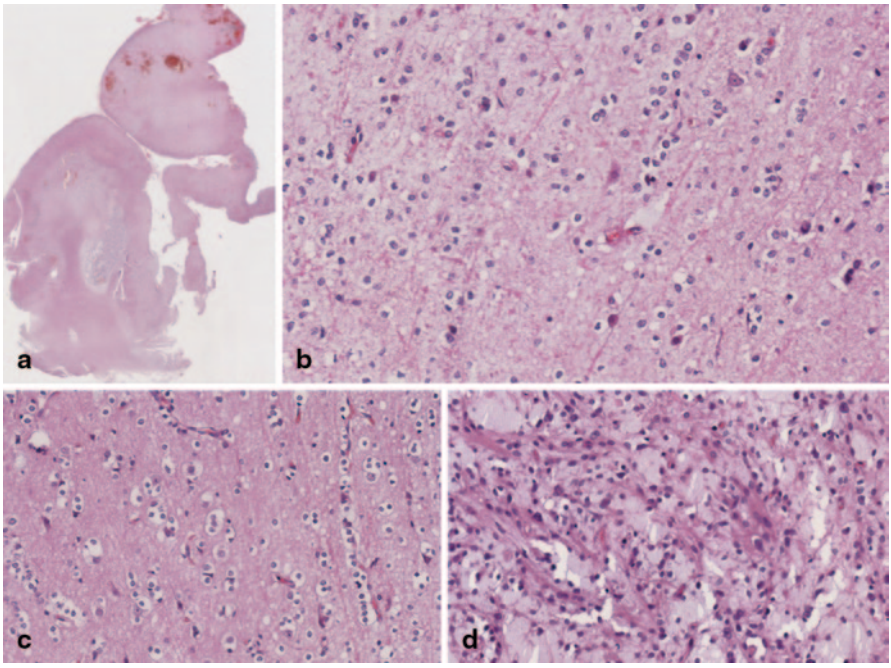

Fig. 6 DNT**a** Low-power of a DNT. **b** H&E, 200x. Bundles of axons and capillaries cross a mucoid matrix, in which some pyramidal neurons float. **c** H&E, 200x. Columns of cells resembling oligodendrocytes line up around axons. **d** H&E, 200x. Some areas may resemble to an pilocytic astrocytoma or ganglioglioma

Mitotic figures are very rare in the typical cases and the proliferative index is low. Although prominent vessels can be seen, endothelial proliferation is generally absent.

Necrosis is unexpected.

These tumors are able to regrow even after apparently complete resections showing a typical or atypical morphology (Daghistani et al. 2013; Schittenhelm et al. 2007). In some cases tumors seem to turn into something similar to anaplastic astrocytomas (Ray et al. 2009), glioblastoma (Duggal et al. 2008; Chuang et al. 2013) or oligoastrocytoma (Gonzales et al. 2007).

Neurocytic Tumors (Extraventricular Neurocytoma)

Neurocytic tumors of the cerebral cortex may cause focal drug-resistant epilepsy (Giulioni et al. 2011). These rare tumors, corresponding to grade II of the WHO Classification, typically appear in the *frontal lobe*, although they can arise in the parietal lobe and, sporadically, in the temporal and occipital lobes (Brat et al. 2001).

Temporal lobe tumors may coexist with FCD (Giulioni et al. 2011).

Neurocytic tumors are well demarcated lesions with variable and nonspecific appearance on neuroimaging studies depending on cellularity and anatomic location. On plain CT scan, they can appear as hypodense or isodense to gray matter; areas of patchy calcifications are common. On MRI, they have been described as hypointense or isointense on T1- and iso- to hyperintense on T2-weighted images with heterogeneous enhancement following the administration of a contrast agent. They commonly display cystic areas and mild to moderate peritumoral edema; intratumoral hemorrhage can occur. DWI studies showed nonspecific features with variable degree of diffusivity. On MRS, strongly decreased or no NAA peak and prominent Cho peak have been reported (Liu et al. 2013; Tortori-Donati et al. 1999; Han et al. 2013; Patil et al. 2014).

The key neuropathological feature is the presence of neurocytes, which are small round cells with modest quantity of cytoplasm, which can look clear, and nuclei with finely granular chromatin and one or more small nucleoli (Fig. 7a, b). Larger ganglioid cells or even larger ganglion cells may be found (Giangaspero et al.

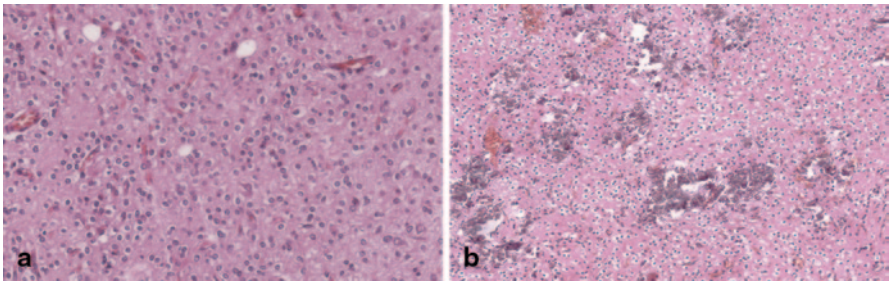

Fig. 7 Neurocytoma. **a** H&E, 200x. Neurocytomas are typically composed of uniform cells, whose clear halo may be prominent. **b** H&E, 100x. Calcifications are common

1997; Tortori-Donati et al. 1999). Tumor cells arrange in sheets, clusters, ribbons, or rosettes, with fine neuropil separating cell aggregates (Scheithauer et al. 2001). Immunohistochemical stainings consistently demonstrate synaptophysin, a major synaptic vesicle protein, in the neurocytes.

Some tumors (gangliogliomas) harbor an astrocytic component.

The mitotic index is generally inconspicuous. Atypical features (high mitotic index, vascular proliferation, necrosis) and high cell proliferation may herald an aggressive clinical behavior.

Multinodular and Vacuolating Neuronal Tumor (MVNT)

This new entity is a purely neuronal tumor of the cerebral hemispheres, which seems to arise mainly from the temporal lobe, displaying a benign clinical behavior. This tumor has been associated with intractable epilepsy (Bodi et al. 2014; Huse et al. 2013).

Surgical Strategies and Complications

Surgery can be considered the treatment of choice for GNTs-related epilepsy. Focal epilepsies caused by GNTs are scarcely responsive to antiepileptic drugs and the surgical treatment of these epileptogenic tumors can offer seizure-freedom in up to 90% of cases (Daumas-Duport et al. 1988; Giulioni et al. 2005; Kirkpatrick et al. 1993).

Furthermore, surgical resection prevents tumor growth and the risk of anaplastic transformation. Last, the surgical approach leads to neuropathological diagnosis.

Although surgery in patients with GNTs-related epilepsy yields a good seizure outcome, the optimal surgical strategy for these tumors has not been fully established. In fact, some authors consider that tumor resection alone (the so-called "lesionectomy") is sufficient to achieve complete seizure control (Bourgeois et al. 2006; Giulioni et al. 2005; Iannelli et al. 2000; Montes et al. 1995). On the other hand, other investigators also recommend the additional resection of peritumoral epileptogenic zones to maximize the seizure outcome (Aronica et al. 2001; Clusmann et al. 2004; Cossu et al. 2008; Morris et al. 1998; Kim et al. 2008; Luyken et al. 2003).

In the surgical management of GNTs, it is of paramount importance to consider some differences between these tumors and other groups of low-grade intra-axial neoplasms. First of all, GNTs are benign tumors in which epilepsy is generally the only clinical feature. Conversely, other types of LGG may present many other clinical findings (intracranial hypertension, focal neurological deficits, etc.). Second, unlike other LGG, GNTs are often located on temporal or temporo-mesial regions. Third, the pathophysiological mechanism of epilepsy in GNTs differs

greatly compared to other LGG. GNTs have a so-called intrinsic epileptogenicity due to their neuronal and glial components. In addition, other epileptogenic diseases (above all, FCD) may be associated with GNTs, may contribute to determine the epileptogenic zone in some patients and are not always well distinguishable from the tumoral tissue on MRI. Finally, in temporal GNTs, the hippocampus may contribute to the epileptogenesis of these lesions even without apparent involvement at MRI or pathological examination (Chang et al. 2008; Englot et al. 2011; Smits and Duffau 2011; van Breemen et al. 2007; Blümcke et al. 2011; Tassi et al. 2002; Giulioni et al. 2009; Schramm and Aliashkevich 2008; Morioka et al. 2007).

Considering these features, the target of surgery for GNTs to obtain the best seizure outcome is not only the anatomical (tumoral) lesion, but the entire epileptogenic zone, which sometimes is larger than the simple structural lesion. Thus, the surgical strategy must be based on the anatomo-electro-clinical correlations that are necessary to identify the epileptogenic zone (Lüders et al. 2006). This principle is particularly important especially for lesions located in the temporal lobe, where the epileptogenic network is usually much more complex and extended than the tumoral area.

Thus, from the surgical point of view, distinctive "philosophies" of treatment may be adopted, usually depending on the location of the tumors.

For lesions located in extratemporal regions the target of surgical resection is the tumoral lesion only. In other words, only a so-called "lesionectomy" is performed (Bourgeois et al. 2006; Montes et al. 1995).

For lesions located in the temporal lobe (the most frequent site of GNTs), several approaches have been described, including lesionectomy, extended lesionectomy, tailored resection and anterior temporal lobectomy (Casazza et al. 1997; Clusmann et al. 2004; Cossu et al. 2008; Jooma et al. 1995; Quarato et al. 2005).

To our knowledge, presently few studies correlate the best surgical strategy to obtain the best seizure outcome to tumor location (Cataltepe et al. 2005; Giulioni et al. 2009; Luyken et al. 2003). There is some consensus that the best seizure outcome for epileptogenic GNTs located in extratemporal and temporo-lateral regions is provided by simple lesionectomy. For temporo-mesial GNTs, the results of a simple lesionectomy are not particularly encouraging, while more extended surgeries (tailored resection) offer better seizure outcomes (Giulioni et al. 2009).

Finally, another important issue concerning the surgical strategy for GNTs is the additional resection of the hippocampal-parahippocampal complex when it is not invaded by GNTs and does not show other signal abnormalities on MR imaging. In fact, if a more extended surgery than simple lesionectomy for temporo-mesial GNTs is a generally accepted concept (Schramm 2008), the correct balance between the extent of resection necessary to provide the best seizure outcome and the avoidance of neuropsychological deficits is still an open problem deserving further studies (Helmstaedter et al. 2011).

Neurosurgery has become safer in the last decades, thanks to the improvement of diagnostic and operative techniques and anaesthesiological procedures.

However, craniotomy and brain surgery imply the risk of complications, whose rate is quite low; mortality is between 0.5 and 1 % (Pilcher and Rusyniak 1993).

The neurosurgical complications of GNTs surgery can be subdivided into craniotomy-related complications (general neurosurgical complications) and complications more specifically related to resective brain surgery.

The first group is represented by hematomas (extradural, subdural, and intracerebral), infections, cerebrospinal fluid leak and, rarely, air embolism and pulmonary embolism. These complications are responsive to appropriate treatment and do not usually influence surgical outcome.

Concerning the second group of complications, we can distinguish between major complications (when severe neurological deficit or daily activity impairment occur) and minor complications (disappearing within 3 months).

Neurological complications depend on the site of resection. Considering that lesionectomy and tailored resection are the surgical strategies commonly adopted in the management of GNTs and these neoplasms are preferentially located in the temporal lobe, typical major neurological complications of temporal lobe surgery (TLS) include contralateral hemiparesis or hemiplegia, homolateral third nerve palsy or paresis, contralateral visual field defects (VFDs) and speech disturbance (Pilcher and Rusyniak 1993; Polkey 2004).

The hemiplegia or hemiparesis can be related mainly to vascular causes (manipulation of middle cerebral artery branches and/or other arteries) (Polkey 2004).

VFD consists classically in superior quadrantanopia contralateral to the resection (Egan et al. 2000). This finding is caused by injury of Meyer's loop (the most anterior part of the optic radiation). Other VFDs in temporal lobe surgery can also occur because of injuries of the optic tract or lateral geniculate body. However VFDs should be considered as an expected event in TLS. Today recent advances in neuroimaging techniques as diffusion tensor imaging (DTI) allowing a better anatomic definition of the optic radiation could contribute to reduce post-resection VFDs.

Other rare complications of TLS include hemorrhage distant from the site of surgery (Toczek et al. 1996; Giulioni et al. 2006; Yacubian et al. 1999), probably due to transmural venous pressure variations (Giulioni and Martinoni 2011) and middle fossa cyst causing raised pressure (Weaver et al. 1996). The global incidence of major neurological complications of TLS is 0.37–4% (Pilcher and Rusyniak 1993; Polkey 2004).

Surgery-related complications in frontal lobe GNTs include hemiparesis if the resection encroaches upon the gyrus anterior to the precentral gyrus. Broca's area must be preserved in the dominant hemisphere. Some authors recommended such resections should be performed under local anaesthesia (Polkey 2004) and/or using a certain number of localizing techniques such as functional MRI and transcranial magnetic stimulation for motor cortex localization (Macdonell et al. 1999).

In spite of these precautions, any resection centered on the central area (primary motor and sensory area) carries the risk of loss of its function.

Resections for lesions located in parietal and posterior temporal regions of dominant hemisphere can determine receptive aphasia, dyslexia, disgraphia and dyscalculia.

Finally, for occipital resections, some degree of VFD(s) can be expected, even if some authors noted that the patients adapted to their VFD within 1 year after surgery (Williamson et al. 1992).

Seizure Outcome

The post-operative seizure outcome is currently assessed according to Engel's Classification (Engel 1996).

The rate of seizure-free outcomes (Engel Class I) in GNTs –related focal epilepsies is about 90%.

Several factors have been correlated with seizure outcome: extension of surgical resection, histotype, duration of epilepsy, age at surgery, association of the tumor with perilesional cortical dysplasia (Aronica et al. 2001; Daumas-Duport et al. 1988; Im et al. 2002; Morris et al. 1998; Nolan et al. 2004).

The main predictor of excellent seizure outcome is the complete removal of the tumor (Morris et al. 1998; Nolan et al. 2004; Khajavi et al. 1995; Kim et al. 2001).

Concerning the completeness of resection, it must be emphasized that only few studies attempted to establish a correlation between tumor site (i.e., temporo-mesial versus temporo-lateral and extra-temporal) and surgical strategy (lesionectomy versus resection of the epileptogenic focus, including the tumor).

Giulioni et al. (2005, 2006) observed that patients affected by extra-temporal and temporo-lateral GNTs had better seizure outcome than those with temporo-mesial GNTs after lesionectomy alone. In addition, in a study comparing retrospectively seizure outcome between two homogeneous series of temporo-mesial epileptogenic GNTs treated respectively by lesionectomy alone and tailored surgery, the same authors reported a much better seizure outcome (93% vs 42.8%) in patients who underwent tailored resection (Giulioni et al. 2009).

These observations and other evidences concerning the role of the temporo-polar cortex in temporal lobe seizures (Chabardès et al. 2005) and the frequent association of GNTs with other epileptogenic abnormalities (Daumas-Duport et al. 2007) suggest that tailored resection for temporo-mesial GNTs is to be preferred to obtain a better seizure outcome.

Future Trends

In the future, optimal therapeutic management of GNTs will need a better understanding of the epileptogenic mechanisms related to these neoplasms.

In addition, further studies are required to elucidate GNTs preference for the temporal lobe.

Neuronal precursors in the subgranular zone of the dentate gyrus and the occurrence of postnatal life neurogenesis have been recently described (González-Martínez et al. 2007; Paradisi et al. 2010; Siebzehnrubl and Blümcke 2008). These data could contribute to explain more complex epileptogenic mechanisms and/or the occurrence of GNTs.

Moreover, the well known association between GNTs and FCD needs further investigations. If common precursor cells for these two diseases can be hypothesized,

either at an embryological stage or during postnatal life, it still remains to be clarified whether FCD coexists with GNTs or has some potential to change into neoplastic cells (Daumas-Duport et al. 2007).

Conclusions

GNTs are one of the most common causes of drug-resistant epilepsy in children and young adults. GNTs-related epilepsies usually respond very well to surgical treatment with an extremely favorable seizure outcome and important effects on cognitive development and patients' quality of life.

Surgical treatment should be planned on the basis of anatomo-electro-clinical correlation defining the epileptogenic zone (which may involve a larger area than the tumor) to be resected.

Tumor location is another important factor (temporo-mesial, temporo-lateral, extratemporal site) to be considered in planning surgical resection.

Finally, even in the event of sporadic seizures and/or seizures responsive to AEDs, surgery should be proposed in order to obtain complete seizure control with freedom from AEDs, and to prevent tumor growth and risk of malignant transformation.

References

Adachi Y, Yagishita A (2008) Gangliogliomas: characteristic imaging findings and role in the temporal lobe epilepsy. Neuroradiology 50:829–834

Allende DS, Prayson RA (2009) The expanding family of glioneuronal tumors. Adv Anat Pathol 16:33–39

Aronica E, Leenstra S, van Veelen CW, van Rijen PC, Hulsebos TJ, Tersmette AC, Yankaya B, Troost D (2001) Glioneuronal tumors and medically intractable epilepsy: a clinical study with long-term follow-up of seizure outcome after surgery. Epilepsy Res 43:179–191

Aronica E, Redeker S, Boer K, Spliet WG, van Rijen PC, Gorter JA, Troost D (2007) Inhibitory networks in epilepsy-associated gangliogliomas and in the perilesional epileptic cortex. Epilepsy Res 74:33–44 (Epub 30 Jan 2007)

Beaumont A, Whittle IR (2000) The pathogenesis of tumour associated epilepsy. Acta Neurochir (Wien) 142:1–15

Becker AJ, Wiestler OD, Figarella-Branger D, Blümcke I (2007) Ganglioglioma and gangliocytoma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon, pp. 103–105

Benifla M, Otsubo H, Ochi A, Weiss SK, Donner EJ, Shroff M, Chuang S, Hawkins C, Drake JM, Elliott I, Smith ML, Snead OC 3rd, Rutka JT (2006) Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. Neurosurgery 59:1203–1214

Bilginer B, Yalnizoglu D, Soylemezoglu F, Turanli G, Cila A, Topçu M, Akalan N (2009) Surgery for epilepsy in children with dysembryoplastic neuroepithelial tumor: clinical spectrum, seizure outcome, neuroradiology, and pathology. Childs Nerv Syst 25:485–491. doi:10.1007/s00381-008-0762-x (Epub 5 Dec 2008)

Blümcke I, Wiestler OD (2002) Gangliogliomas: an intriguing tumor entity associated with focal epilepsies. J Neuropathol Exp Neurol 61:575–584

Blümcke I, Luyken C, Urbach H, Schramm J, Wiestler OD (2004) An isomorphic subtype of long-term epilepsy-associated astrocytomas associated with benign prognosis. Acta Neuropathol 107:381–388

Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R (2011) The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 52:158–174. doi:10.1111/j.1528-1167.2010.02777.x (Epub 10 Nov 2010)

Bodi I, Selway R, Bannister P, Doey L, Mullatti N, Elwes R, Honavar M (2012) Diffuse form of dysembryoplastic neuroepithelial tumour: the histological and immunohistochemical features of a distinct entity showing transition to dysembryoplastic neuroepithelial tumour and ganglioglioma. Neuropathol Appl Neurobiol 38:411–425

Bodi I, Curran O, Selway R, Elwes R, Burrone J, Laxton R, Al-Sarraj S, Honavar M (2014) Two cases of multinodular and vacuolating neuronal tumour. Acta Neuropathol Commun 2:7

Bourgeois M, Di Rocco F, Sainte-Rose C (2006) Lesionectomy in the pediatric age. Childs Nerv Syst 22:931–935 (Epub 5 July 2006)

Brat DJ, Scheithauer BW, Eberhart CG, Burger PC (2001) Extraventricular neurocytomas: pathologic features and clinical outcome. Am J Surg Pathol 25:1252–1260

Bulakbasi N, Kocaoglu M, Sanal TH, Tayfun C (2007) Dysembryoplastic neuroepithelial tumors: proton MR spectroscopy, diffusion and perfusion characteristics. Neuroradiology 49:805–812

Campos AR, Clusmann H, von Lehe M, Niehusmann P, Becker AJ, Schramm J, Urbach H (2009) Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. Neuroradiology 51:433–443

Casazza M, Avanzini G, Broggi G, Fornari M, Franzini A (1989) Epilepsy course in cerebral gangliogliomas: a study of 16 cases. Acta Neurochir Suppl (Wien) 46:17–20

Casazza M, Avanzini G, Ciceri E, Spreafico R, Broggi G (1997) Lesionectomy in epileptogenic temporal lobe lesions: preoperative seizure course and postoperative outcome. Acta Neurochir Suppl 68:64–69

Castillo M (1998) Gangliogliomas: ubiquitous or not? AJNR Am J Neuroradiol 19:807–809

Castillo M, Davis PC, Takei Y, Hoffman JC (1990) Intracranial ganglioglioma: MR, CT, and clinical findings in 18 patients. AJNR Am J Neuroradiol 11:109–114

Cataltepe O, Turanli G, Yalnizoglu D, Topçu M, Akalan N (2005) Surgical management of temporal lobe tumor-related epilepsy in children. J Neurosurg 102:280–287

Chabardès S, Kahane P, Minotti L, Tassi L, Grand S, Hoffmann D, Benabid AL (2005) The temporopolar cortex plays a pivotal role in temporal lobe seizures. Brain 128:1818–1831 (Epub 27 April 2005)

Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, Berger MS (2008) Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 108:227–235. doi:10.3171/JNS/2008/108/2/0227

Chang EF, Christie C, Sullivan JE, Garcia PA, Tihan T, Gupta N, Berger MS, Barbaro NM (2010) Seizure control outcomes after resection of dysembryoplastic neuroepithelial tumor in 50 patients. J Neurosurg Pediatr 5:123–130. doi:10.3171/2009.8.PEDS09368

Chassoux F, Daumas-Duport C (2013) Dysembryoplastic neuroepithelial tumors: where are we now? Epilepsia 54:129–134. doi:10.1111/epi.12457

Chassoux F, Devaux B, Landré E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Daumas-Duport C (2000) Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain 123:1733–1751

Chassoux F, Rodrigo S, Mellerio C, Landré E, Miquel C, Turak B, Laschet J, Meder JF, Roux FX, Daumas-Duport C, Devaux B (2012) Dysembryoplastic neuroepithelial tumors: an MRI-based scheme for epilepsy surgery. Neurology 79:1699–1707

Chuang NA, Yoon JM, Newbury RO, Crawford JR (2013) Glioblastoma multiforme arising from dysembryoplastic neuroepithelial tumor in a child in the absence of therapy. J Pediatr Hematol Oncol (4 Dec) [Epub ahead of print]

Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, Haun D, Elger CE (2002) Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg 97:1131–1141

Clusmann H, Kral T, Gleissner U, Sassen R, Urbach H, Blümcke I, Bogucki J, Schramm J (2004) Analysis of different types of resection for pediatric patients with temporal lobe epilepsy. Neurosurgery 54:847–860

Consales A, Striano P, Nozza P, Morana G, Ravegnani M, Piatelli G, Pavanello M, Zoli ML, Baglietto MG, Cama A (2013) Glioneuronal tumors and epilepsy in children: seizure outcome related to lesionectomy. Minerva Pediatr 65:609–616

Cossu M, Lo Russo G, Francione S, Mai R, Nobili L, Sartori I, Tassi L, Citterio A, Colombo N, Bramerio M, Galli C, Castana L, Cardinale F (2008) Epilepsy surgery in children: results and predictors of outcome on seizures. Epilepsia 49:65–72 (Epub 21 July 2007)

Daghistani R, Miller E, Kulkarni AV, Widjaja E (2013) Atypical characteristics and behavior of dysembryoplastic neuroepithelial tumors. Neuroradiology 55:217–224

Daumas-Duport C (1993) Dysembryoplastic neuroepithelial tumors. Brain Pathol 3:255–268

Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER Jr, Vedrenne C (1988) Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Neurosurgery 23:545–556

Daumas-Duport C, Pietsch T, Hawkins C, Shankar SK (2007) Dysembryoplastic neuroepithelial tumour. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon, pp 99–102

de Groot M, Toering ST, Boer K, Spliet WG, Heimans JJ, Aronica E, Reijneveld JC (2010) Expression of synaptic vesicle protein 2A in epilepsy-associated brain tumors and in the peritumoral cortex. Neuro Oncol 12:265–273. doi:10.1093/neuonc/nop028 (Epub 6 Jan 2010)

Duggal N, Taylor R, Zou GY, Hammond RR (2008) Dysembryoplastic neuroepithelial tumours: clinical, proliferative and apoptotic features. J Clin Pathol 61:127–131

Egan RA, Shults WT, So N, Burchiel K, Kellogg JX, Salinsky M (2000) Visual field deficits in conventional anterior temporal lobectomy versus amygdalohippocampectomy. Neurology 55:1818–1822

Engel J Jr (1996) Surgery for seizures. N Engl J Med 334:647–652

Englot DJ, Berger MS, Barbaro NM, Chang EF (2011) Predictors of seizure freedom after resection of supratentorial low-grade gliomas. A review. J Neurosurg 115:240–244. doi:10.3171/2011.3.JNS1153 (Epub 29 April 2011)

Ferrier CH, Aronica E, Leijten FS, Spliet WG, van Huffelen AC, van Rijen PC, Binnie CD (2006) Electrocorticographic discharge patterns in glioneuronal tumors and focal cortical dysplasia. Epilepsia 47:1477–1486

Gaggero R, Consales A, Fazzini F, Mancardi MM, Baglietto MG, Nozza P, Rossi A, Pistorio A, Tumolo M, Cama A, Garrè ML, Striano P (2009) Epilepsy associated with supratentorial brain tumors under 3 years of life. Epilepsy Res 87:184–189. doi:10.1016/j.eplepsyres.2009.08.012 (Epub 23 Sept 2009)

Giangaspero F, Cenacchi G, Losi L, Cerasoli S, Bisceglia M, Burger PC (1997) Extraventricular neoplasms with neurocytoma features. A clinicopathological study of 11 cases. Am J Surg Pathol 21:206–212

Giulioni M, Martinoni M (2011) Postoperative intracranial haemorrhage and remote cerebellar haemorrhage. Neurosurg Rev 34:523–525. doi:10.1007/s10143-011-0335-4 (Epub 15 June 2011)

Giulioni M, Galassi E, Zucchelli M, Volpi L (2005) Seizure outcome of lesionectomy in glioneuronal tumors associated with epilepsy in children. J Neurosurg 102:288–293

Giulioni M, Gardella E, Rubboli G, Roncaroli F, Zucchelli M, Bernardi B, Tassinari CA, Calbucci F (2006) Lesionectomy in epileptogenic gangliogliomas: seizure outcome and surgical results. J Clin Neurosci 13:529–535

Giulioni M, Rubboli G, Marucci G, Martinoni M, Volpi L, Michelucci R, Marliani AF, Bisulli F, Tinuper P, Castana L, Sartori I, Calbucci F (2009) Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomesial glioneuronal tumors: lesionectomy compared with tailored resection. J Neurosurg 111:1275–1282. doi:10.3171/2009.3.JNS081350

Giulioni M, Martinoni M, Rubboli G, Marucci G, Marliani AF, Battaglia S, Badaloni F, Pozzati E, Calbucci F (2011) Temporo-mesial extraventricular neurocytoma and cortical dysplasia in focal temporal lobe epilepsy. J Clin Neurosci 18:147–148

Gonzales M, Dale S, Susman M, Nolan P, Ng WH, Maixner W, Laidlaw J (2007) Dysembryoplastic neuroepithelial tumor (DNT)-like oligodendrogliomas or Dnts evolving into oligodendrogliomas: two illustrative cases. Neuropathology 27:324–330

González-Martínez JA, Bingaman WE, Toms SA, Najm IM (2007) Neurogenesis in the postnatal human epileptic brain. J Neurosurg 107:628–635

Hall WA, Yunis EJ, Albright AL (1986) Anaplastic ganglioglioma in an infant: case report and review of the literature. Neurosurgery 19:1016–1020

Hammond RR, Duggal N, Woulfe JM, Girvin JP (2000) Malignant transformation of a dysembryoplastic neuroepithelial tumor. Case report. J Neurosurg 92:722–725

Han L, Niu H, Wang J, Wan F, Shu K, Ke C, Lei T (2013) Extraventricular neurocytoma in pediatric populations: a case report and review of the literature. Oncol Lett 6:1397–1405

Helmstaedter C, Roeske S, Kaaden S, Elger CE, Schramm J (2011) Hippocampal resection length and memory outcome in selective epilepsy surgery. J Neurol Neurosurg Psychiatry 82:1375–1381 doi:10.1136/jnnp.2010.240176 (Epub 7 June 2011)

Honavar M, Janota I, Polkey CE (1999) Histological heterogeneity of dysembryoplastic neuroepithelial tumour: identification and differential diagnosis in a series of 74 cases. Histopathology 34:342–356

Huse JT, Edgar M, Halliday J, Mikolaenko I, Lavi E, Rosenblum MK (2013) Multinodular and vacuolating neuronal tumors of the cerebrum: 10 cases of a distinctive seizure-associated lesion. Brain Pathol 23:515–524

Iannelli A, Guzzetta F, Battaglia D, Iuvone L, Di Rocco C (2000) Surgical treatment of temporal tumors associated with epilepsy in children. Pediatr Neurosurg 32:248–254

Im SH, Chung CK, Cho BK, Wang KC, Yu IK, Song IC, Cheon GJ, Lee DS, Kim NR, Chi JG (2002) Intracranial ganglioglioma: preoperative characteristics and oncologic outcome after surgery. J Neurooncol 59:173–183

Jay V, Squire J, Becker LE, Humphreys R (1994) Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components. Report of a case with flow cytometric and cytogenetic analysis. Cancer 73:2862–2868

Johnson JH Jr, Hariharan S, Berman J, Sutton LN, Rorke LB, Molloy P, Phillips PC (1997) Clinical outcome of pediatric gangliogliomas: ninety-nine cases over 20 years. Pediatr Neurosurg 27:203–207

Jooma R, Yeh HS, Privitera MD, Gartner M (1995) Lesionectomy versus electrophysiologically guided resection for temporal lobe tumors manifesting with complex partial seizures. J Neurosurg 83:231–236

Kerkhof M, Vecht CJ (2013) Seizure characteristics and prognostic factors of gliomas. Epilepsia 54:12–17. doi:10.1111/epi.12437

Khajavi K, Comair YG, Prayson RA, Wyllie E, Palmer J, Estes ML, Hahn JF (1995) Childhood ganglioglioma and medically intractable epilepsy. A clinicopathological study of 15 patients and a review of the literature. Pediatr Neurosurg 22:181–188

Kim SK, Wang KC, Hwang YS, Kim KJ, Cho BK (2001) Intractable epilepsy associated with brain tumors in children: surgical modality and outcome. Childs Nerv Syst 17:445–452

Kim NR, Wang KC, Bang JS, Choe G, Park Y, Kim SK, Cho BK, Chi JG (2003) Glioblastomatous transformation of ganglioglioma: case report with reference to molecular genetic and flow cytometric analysis. Pathol Int 53:874–882

Kim SK, Wang KC, Hwang YS, Kim KJ, Chae JH, Kim IO, Cho BK (2008) Epilepsy surgery in children: outcomes and complications. J Neurosurg Pediatr 1:277–283. doi:10.3171/PED/2008/1/4/277

Kirkpatrick PJ, Honavar M, Janota I, Polkey CE (1993) Control of temporal lobe epilepsy following en bloc resection of low-grade tumors. J Neurosurg 78:19–25

Kleihues P, Cavenee WK (eds) (2000) Pathology and genetics of tumours of the nervous system. International Agency for Research on Cancer, Lyon

Lawson JA, Duchowny MS (2004) Paediatric epilepsy surgery. In: Shorvon SD, Perucca E, Fish DR, Dodson WE (eds) The treatment of epilepsy, 2nd edn. Blackwell Publishing, Oxford, pp 779–789

Lee MC, Kang JY, Seol MB, Kim HS, Woo JY, Lee JS, Jung S, Kim JH, Woo YJ, Kim MK, Kim HI, Kim SU (2006) Clinical features and epileptogenesis of dysembryoplastic neuroepithelial tumor. Childs Nerv Syst 22:1611–1618 (Epub 30 Aug 2006)

Lellouch-Tubiana A, Bourgeois M, Vekemans M, Robain O (1995) Dysembryoplastic neuroepithelial tumors in two children with neurofibromatosis type 1. Acta Neuropathol 90:319–322

Liu K, Wen G, Lv XF, Deng YJ, Deng YJ, Hou GQ, Zhang XL, Han LJ, Ding JL (2013) MR imaging of cerebral extraventricular neurocytoma: a report of 9 cases. AJNR Am J Neuroradiol 34:541–546

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007a) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109 (Epub 6 July 2007)

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007b) WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon

Lüders HO, Najm I, Nair D, Widdess-Walsh P, Bingman W (2006) The epileptogenic zone: general principles. Epileptic Disord 8:S1–S9 (Erratum in: Epileptic Disord 2008, 10, 191)

Luyken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, Schramm J (2003) The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia 44:822–830

Luyken C, Blümcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J (2004) Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer 101:146–155

Macdonell RA, Jackson GD, Curatolo JM, Abbott DF, Berkovic SF, Carey LM, Syngeniotin A, Fabinyi GC, Scheffer IE (1999) Motor cortex localization using functional MRI and transcranial magnetic stimulation. Neurology 53:1462–1467

Minkin K, Klein O, Mancini J, Lena G (2008) Surgical strategies and seizure control in pediatric patients with dysembryoplastic neuroepithelial tumors: a single-institution experience. J Neurosurg Pediatr 1:206–210. doi:10.3171/PED/2008/1/3/206

Montes JL, Rosenblatt B, Farmer JP, O'Gorman AM, Andermann F, Watters GV, Meagher-Villemure K (1995) Lesionectomy of MRI detected lesions in children with epilepsy. Pediatr Neurosurg 22:167–173

Morioka T, Hashiguchi K, Nagata S, Miyagi Y, Yoshida F, Shono T, Mihara F, Koga H, Sasaki T (2007) Additional hippocampectomy in the surgical management of intractable temporal lobe epilepsy associated with glioneuronal tumor. Neurol Res 29:807–815

Morris HH, Matkovic Z, Estes ML, Prayson RA, Comair YG, Turnbull J, Najm I, Kotagal P, Wyllie E (1998) Ganglioglioma and intractable epilepsy: clinical and neurophysiologic features and predictors of outcome after surgery. Epilepsia 39:307–313

Nolan MA, Sakuta R, Chuang N, Otsubo H, Rutka JT, Snead OC 3rd, Hawkins CE, Weiss SK (2004) Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. Neurology 62:2270–2276

Obeid M, Wyllie E, Rahi AC, Mikati MA (2009) Approach to pediatric epilepsy surgery: State of the art, Part II: Approach to specific epilepsy syndromes and etiologies. Eur J Paediatr Neurol 13:115–127. doi:10.1016/j.ejpn.2008.05.003

Ostertun B, Wolf HK, Campos MG, Matus C, Solymosi L, Elger CE, Schramm J, Schild HH (1996) Dysembryoplastic neuroepithelial tumors: MR and CT evaluation. AJNR Am J Neuroradiol 17:419–430

Otsubo H, Hoffman HJ, Humphreys RP, Hendrick EB, Drake JM, Hwang PA, Becker LE, Chuang SH (1990–1991) Evaluation, surgical approach and outcome of seizure patients with gangliogliomas. Pediatr Neurosurg 16:208–212

Ozlen F, Gunduz A, Asan Z, Tanriverdi T, Ozkara C, Yeni N, Yalcinkaya C, Ozyurt E, Uzan M (2010) Dysembryoplastic neuroepithelial tumors and gangliogliomas: clinical results of 52 patients. Acta Neurochir (Wien) 152:1661–1671. doi:10.1007/s00701-010-0696-4 (Epub 5 June 2010)

Paradisi M, Fernández M, Del Vecchio G, Lizzo G, Marucci G, Giulioni M, Pozzati E, Antonelli T, Lanzoni G, Bagnara GP, Giardino L, CalzÃ L (2010) Ex vivo study of dentate gyrus neurogenesis in human pharmacoresistant temporal lobe epilepsy. Neuropathol Appl Neurobiol 36(6):535–550. doi:10.1111/j.1365-2990.2010.01102.x (Oct 2010)

Patil AS, Menon G, Easwer HV, Nair S (2014) Extraventricular neurocytoma, a comprehensive review. Acta Neurochir (Wien) 156: 349–354. doi:10.1007/s00701-013-1971-y (Epub 20 Dec 2013)

Pilcher WH, Rusyniak WG (1993) Complications of epilepsy surgery. Neurosurg Clin N Am 4:311–325

Polkey CE (2004) Complications of epilepsy surgery. In: Shorvon SD, Perucca E, Fish DR, Dodson WE (eds) The treatment of epilepsy, 2nd edn. Blackwell Publishing, Oxford, 849–860

Prayson RA (1999) Composite ganglioglioma and dysembryoplastic neuroepithelial tumor. Arch Pathol Lab Med 123:247–250

Prayson RA, Napekoski KM (2012) Composite ganglioglioma/dysembryoplastic neuroepithelial tumor: a clinicopathologic study of 8 cases. Hum Pathol 43:1113–1118

Prayson RA, Khajavi K, Comair YG (1995) Cortical architectural abnormalities and MIB1 immunoreactivity in gangliogliomas: a study of 60 patients with intracranial tumors. J Neuropathol Exp Neurol 54:513–520

Prayson RA, Morris HH, Estes ML, Comair YG (1996) Dysembryoplastic neuroepithelial tumor: a clinicopathologic and immunohistochemical study of 11 tumors including MIB1 immunoreactivity. Clin Neuropathol 15:47–53

Prayson RA, Fong J, Najm I (2010) Coexistent pathology in chronic epilepsy patients with neoplasms. Mod Pathol 23:1097–1103. doi:10.1038/modpathol.2010.94 (Epub 21 May 2010)

Quarato PP, Di Gennaro G, Mascia A, Grammaldo LG, Meldolesi GN, Picardi A, GiampÃ T, Falco C, Sebastiano F, Onorati P, Manfredi M, Cantore G, Esposito V (2005) Temporal lobe epilepsy surgery: different surgical strategies after a non-invasive diagnostic protocol. J Neurol Neurosurg Psychiatry 76:815–824

Ray WZ, Blackburn SL, Casavilca-Zambrano S, Barrionuevo C, Orrego JE, Heinicke H, Dowling JL, Perry A (2009) Clinicopathologic features of recurrent dysembryoplastic neuroepithelial tumor and rare malignant transformation: a report of 5 cases and review of the literature. J Neurooncol 94:283–292

Raybaud C, Shroff M, Rutka JT, Chuang SH (2006) Imaging surgical epilepsy in children. Childs Nerv Syst 22:786–809

Rojiani AM, Emery JA, Anderson KJ, Massey JK (1996) Distribution of heterotopic neurons in normal hemispheric white matter: a morphometric analysis. J Neuropathol Exp Neurol 55:178–183

Rossi GF, Pompucci A, Colicchio G, Scerrati M (1999) Factors of surgical outcome in tumoural epilepsy. Acta Neurochir (Wien) 141:819–824

Scheithauer BW, Eberhart CG, Burger PC (2001) Extraventricular neurocytomas: pathologic features and clinical outcome. Am J Surg Pathol 25:1252–1260

Schittenhelm J, Mittelbronn M, Wolff M, Truebenbach J, Will BE, Meyermann R, Beschorner R (2007) Multifocal dysembryoplastic neuroepithelial tumor with signs of atypia after regrowth. Neuropathology 27:383–389

Schmitz AK, Grote A, Raabe A, Urbach H, Friedman A, von Lehe M, Becker AJ, Niehusmann P (2013) Albumin storage in neoplastic astroglial elements of gangliogliomas. Seizure 22:144–150

Schramm J (2008) Temporal lobe epilepsy surgery and the quest for optimal extent of resection: a review. Epilepsia 49:1296–1307. doi:10.1111/j.1528-1167.2008.01604.x (Epub 11 April 2008)

Schramm J, Aliashkevich AF (2008) Temporal mediobasal tumors: a proposal for classification according to surgical anatomy. Acta Neurochir (Wien) 150:857–864. doi:10.1007/s00701-008-0013–7 (Epub 23 Aug 2008)

Selvanathan SK, Hammouche S, Salminen HJ, Jenkinson MD (2011) Outcome and prognostic features in anaplastic ganglioglioma: analysis of cases from the SEER database. J Neurooncol 105:539–545

Sharma MC, Jain D, Gupta A, Sarkar C, Suri V, Garg A, Gaikwad SB, Chandra PS (2009) Dysembryoplastic neuroepithelial tumor: a clinicopathological study of 32 cases. Neurosurg Rev 32:161–170. doi:10.1007/s10143-008-0181-1 (Epub 23 Jan 2009)

Siebzehnrubl FA, Blümcke I (2008) Neurogenesis in the human hippocampus and its relevance to temporal lobe epilepsies. Epilepsia 49:55–65. doi:10.1111/j.1528-1167.2008.01638.x

Smits A, Duffau H (2011) Seizures and the natural history of World Health Organization Grade II gliomas: a review. Neurosurgery 68:1326–1333. doi:10.1227/NEU.0b013e31820c3419

Soffer D, Lach B, Constantini S (1992) Melanotic cerebral ganglioglioma: evidence for melanogenesis in neoplastic astrocytes. Acta Neuropathol 83:315–323

Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Bramerio M, Citterio A, Spreafico R (2002) Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 125:1719–1732

Thom M, Toma A, An S, Martinian L, Hadjivassiliou G, Ratilal B, Dean A, McEvoy A, Sisodiya SM, Brandner S (2011) One hundred and one dysembryoplastic neuroepithelial tumors: an adult epilepsy series with immunohistochemical, molecular genetic, and clinical correlations and a review of the literature. J Neuropathol Exp Neurol 70:859–878

Toczek MT, Morrell MJ, Silverberg GA, Lowe GM (1996) Cerebellar hemorrhage complicating temporal lobectomy. Report of four cases. J Neurosurg 85:718–722

Tortori-Donati P, Fondelli MP, Rossi A, Cama A, Brisigotti M, Pellicanò G (1999) Extraventricular neurocytoma with ganglionic differentiation associated with complex partial seizures. AJNR Am J Neuroradiol 20:724–727

van Breemen MS, Wilms EB, Vecht CJ (2007) Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 6:421–430

Ventureyra E, Herder S, Mallya BK, Keene D (1986) Temporal lobe gangliogliomas in children. Childs Nerv Syst 2:63–66

Weaver JP, Phillips C, Horowitz SL, Benjamin S (1996) Middle fossa cyst presenting as a delayed complication of temporal lobectomy: case report. Neurosurgery 38:1047–1051

Wetjen NM, Radhakrishnan K, Cohen-Gadol AA, Cascino G (2004) Resective surgery of neoplastic lesions for epilepsy. In: Shorvon SD, Perucca E, Fish DR, Dodson WE (eds) The treatment of epilepsy, 2nd edn. Blackwell Publishing, Oxford, pp 728–741

Williamson PD, Thadani VM, Darcey TM, Spencer DD, Spencer SS, Mattson RH (1992) Occipital lobe epilepsy: clinical characteristics, seizure spread patterns, and results of surgery. Ann Neurol 31:3–13

Wolf HK, Müller MB, Spänle M, Zentner J, Schramm J, Wiestler OD (1994) Ganglioglioma: a detailed histopathological and immunohistochemical analysis of 61 cases. Acta Neuropathol 88:166–173

Yacubian EM, de Andrade MM, Jorge CL, Valério RM (1999) Cerebellar hemorrhage after supratentorial surgery for treatment of epilepsy: report of three cases. Neurosurgery 45:159–162

Zaghloul KA, Schramm J (2011) Surgical management of glioneuronal tumors with drug-resistant epilepsy. Acta Neurochir (Wien) 153:1551–1559. doi:10.1007/s00701-011-1050-1 (Epub 21 May 2011)

Zentner J, Wolf HK, Ostertun B, Hufnagel A, Campos MG, Solymosi L, Schramm J (1994) Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psychiatry 57:1497–1502

Zhang D, Henning TD, Zou LG, Hu LB, Wen L, Feng XY, Dai SH, Wang WX, Sun QR, Zhang ZG (2008) Intracranial ganglioglioma: clinicopathological and MRI findings in 16 patients. Clin Radiol 63:80–91

Zhang JG, Hu WZ, Zhao RJ, Kong LF (2013) Dysembryoplastic neuroepithelial tumor: a clinical, neuroradiological, and pathological study of 15 Cases. J Child Neurol (10 June) [Epub ahead of print]