Review article

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Epilepsy-associated tumours: what epileptologists should know about neuropathology, terminology, and classification systems

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ABSTRACT – Brain tumours are an ever-challenging issue in neurology and related medical disciplines. This applies in particular to brain tumours associated with childhood-onset epilepsies, in which seizures are the presenting and only neurological symptom, as our current understanding of the biology and clinical behaviour of an individual tumour is far from being evidence-based. Prospective and randomized clinical trials are lacking in the field of epilepsy-associated tumours and a review of the current literature evokes more questions than provides answers. In this review, current areas of controversy in neuropathology, as well as terminology and classification, are discussed from an epileptologist's perspective. An illustrative case report exemplifies this controversy to further promote interdisciplinary discussion and novel research avenues towards comprehensive patient management in the near future.

Key words: seizure, neuropathology, epileptology, neuro-oncology, neurosurgery, classification, glioma, ganglioglioma, dysembryoplastic neuroepithelial tumour, long-term epilepsy associated tumour (LEAT)

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Benign and epilepsy-associated neuro-epithelial brain tumours comprise only 2-5% of tumours of the central nervous system (Jemal *et al.,* 2006), although the exact incidence and prevalence has not yet been established. They represent, however, the second most frequent category of focal pathology in epilepsy surgery series, both in adults (after hippocampal sclerosis) (Blümcke *et al.,* 2014, 2015) and children (after focal cortical dysplasia) (Harvey *et al.,* 2008; Blümcke *et al.,* 2015). These tumours have been previously termed "LEATs" (long-term epilepsy associated tumours) (Luyken *et al.,* 2003), and patients are considered successful surgical candidates, with 60-100% of patients

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becoming seizure-free following epilepsy surgery (reviews in Giulioni *et al.,* 2009; Englot *et al.,* 2012; Thom *et al.,* 2012; Bonney *et al.,* 2015, 2016). What makes the epilepsy surgery of a patient with a LEAT different from epilepsy surgery in other aetiologies, *e.g.* such as focal cortical dysplasia, is the oncological aspect. Yet, most LEATs are classified as WHO grade I with very low risk of tumour progression and malignant transformation, *e.g.* less than 1% for dysembryoplastic neuroepithelial tumours (DNT) (Thom *et al.,* 2011) and only slightly higher for gangliogliomas (GGs) and pilocytic astrocytomas (PAs) (Thom *et al.,* 2011, 2012). Rates of progression and malignant transformation for WHO grade II brain tumours are also considered lower in children compared to adults, in particular when associated with seizures (van Veelen *et al.,* 1998; Majores *et al.,* 2008). The histopathological classification of LEATs remains, however, difficult and requires special expertise (Blümcke *et al.,* 2014). Allocating a WHO grade to a LEAT that is too low will carry the risk for a patient of not undergoing mandatory long-term tumour surveillance; allocating a WHO grade that is too high will put the patient at unnecessary exposure to life-threatening radiotherapy and/or chemotherapy (*see illustrative case below*). Epileptologists should also be aware that the refinement of tumour classification continues to evolve towards personalised medicine, with "targeted therapy" (Louis *et al.,* 2014, 2016a). Up-to-date neuropathological investigations, including brain banking for *post hoc* molecular studies, are not always available and the recently proposed "international recommendation for a comprehensive neuropathological work-up" will be most helpful to standardise laboratory practice throughout the world's community of epileptology (Blümcke *et al.,* 2016).

Heterogeneous terminology for WHO grade I and II brain tumours

Consulting the literature to better understand neuropathology-based terminology and principles of tumour classification can be a challenging and also confusing experience! As a common example, WHO grade I and II brain tumours are often lumped together under the umbrella "benign brain tumours", whereas this term is not used for the WHO classification of tumours of the central nervous system. The WHO's grading system is a malignancy scale for a wide range of neoplasms rather than based on a strict histological definition (Louis *et al.,* 2007a). WHO grade I should be applied to lesions with low proliferative potential and with a possibility to be cured by surgical resection. WHO grade II is designated to neoplasms, which are generally infiltrative in nature and, despite low-level proliferative activity, often recur (Louis *et al.,* 2007b). Transformation to higher malignancy is not rare in certain types of WHO grade II tumours, therefore they should still be regarded as *relatively* benign, *i.e.* compared to glioblastoma multiforme WHO grade IV.

Another challenging issue arises when "low-grade" is used in conjunction with "glioma". One should be aware of, and accept, the fact that "glioma" is a descriptive term and not a neuropathological diagnosis. The inclusion of histological subgroups in reports on "low-grade gliomas" can vary greatly, *e.g.* dealing exclusively with WHO grade II astrocytomas, oligodendrogliomas and oligoastrocytomas, or preferentially with WHO grade I PAs (Chang *et al.,* 2008; Jakola *et al.,* 2012; Pallud *et al.,* 2014; You *et al.,* 2012). Some other reports annotating "low-grade gliomas" may include WHO grade I and II tumours with astroglial lineage plus oligodendrogliomas and oligoastrocytomas, as well as glio-neuronal tumours, such as GGs and DNTs (Fouladi *et al.,* 2003; Sievert and Fisher, 2009; Ruda *et al.,* 2012; Bandopadhayay *et al.,* 2014; Bergthold *et al.,* 2014).

Occasionally, grading of "gliomas" is not even mentioned and further reading is necessary to elucidate the biological nature of the tumours studied, *e.g.* when gliomas are reported as "low-grade infiltrative" or "diffuse low-grade" (Smith *et al.,* 2008; Schucht *et al.,* 2013; Pallud *et al.,* 2014) they should be considered as WHO grade II. Less ambiguous than the term "glioma" is the term "glio-neuronal tumours" (Wolf *et al.,* 1995; Aronica *et al.,* 2001; Ferrier *et al.,* 2006; Giulioni *et al.,* 2009; Englot *et al.,* 2012; Lin *et al.,* 2012) or "mixed glio-neuronal tumours" (Luyken *et al.,* 2003) for a group of predominantly benign brain tumours defined by the WHO as "neuronal and mixed neuronal-glial tumours" (Louis *et al.,* 2007b).

Although it was stated by David Louis *et al.* (2007) that "the Working Group (on behalf of the WHO) distinguished between *clinico-pathological entities*, *variants of entities* and *histological patterns*" of (all the) brain tumours, the observation that certain brain tumours are almost always associated with epilepsy and that seizures are rather rare in other tumour types is left aside in the WHO classification. An edition of the current 2007 WHO classification has been released in May 2016 but does still not address this important clinical issue (Louis *et al.,* 2016b) (*discussed below*). In fact, seizures are often the only neurological sign in benign brain tumours and it is the epilepsy which affects a patient's quality of life. Furthermore, surgical resection of a low-grade glio-neuronal tumour (WHO grade I) may not even be justified unless the epilepsy is also cured.

The term "LEAT" has been coined by the University of Bonn Epilepsy Group (Luyken *et al.,* 2003) to distinguish this particular group of tumours from those

Table 1. Glial and glio-neuronal tumours (WHO classification from 2007) frequently encountered in epilepsy surgery.

GLIO-NEURONAL TUMOURS (WHO classification 2007)	**Acronym**	**WHO grading**	Comments
Ganglioglioma	GG	WHO I°/III°	The concept of atypical WHO II° is not supported by the WHO classification.
Gangliocytoma	GC	WHO I°	
Dysembryoblastic neuro-epithelial tumour	DNT	WHO I°	
Papillary glio-neuronal tumour	PGNT	WHO I°	
Rosette-forming glio-neuronal tumour	RGNT	WHO I°	
Glio-neuronal tumour with neuropil islands	GNTNI	WHO II°/III°	
GLIAL TUMOURS (WHO classification 2007)			
Pilocytic astrocytoma	PA	WHO I°/III°	
Pleomorphic xanthoastrocytoma	PXA	WHO II°/III°	
Diffuse astrocytoma	DA	WHO II°	
Oligodendroglioma	O	WHO II°	
Angiocentric glioma	ANET	WHO I°	

brain tumours in which epilepsy is merely an epiphenomenon; the former are associated with:
– young age at onset of seizures, and seizures as the only presenting symptom and;
– slow growth and neocortical localization, preferentially within the temporal lobes.
LEATs were then subdivided by Thom *et al*. (2012) into two categories, according to their specific histopathological patterns of differentiation (*table 1*).
Papillary glioneuronal tumour (PGNT), rosette-forming glioneuronal tumour (RGNT), glioneuronal tumour with neuropil-like islands (GNTNI), and angiocentric neuroepithelial tumour (ANET) have been recognised only very recently as distinct tumours with benign behaviour (Louis *et al.,* 2007b), and represent even more rare entities (Williams *et al.,* 2008; Shakur *et al.,* 2009; Takada *et al.,* 2011; Agarwal *et al.,* 2012; Alexandru *et al.,* 2013; Demetriades *et al.,* 2013; Schlamann *et al.,* 2014; Ni *et al.,* 2015).
The term "LEAT", though widely accepted nowadays, will continue to impede the epileptologist's effort to cure epilepsy in patients with benign brain tumours. However, a minimum of two years of epilepsy was the inclusion criterion for epilepsy surgery patients in the original study by Luyken *et al.,* 2003. Other terms sometimes used for these tumours is "epilom" (Duncan and de Tisi, 2013), "epileptoma" (Japp *et al.,* 2013), or "epilepsoma" (P. Kahane, personal communication). It is beyond the scope of this review to establish a better terminology for this tumour spectrum; this will be targeted by the current ILAE Task Force for Neuropathology. Why these tumours have such epileptogenic potential is also beyond the scope of this review and will not be discussed further in this article (Blümcke *et al.,* 2014; Thom *et al.,* 2012; Pallud *et al.,* 2013).

Variation in the *histological* classification of LEATs

It is also puzzling and difficult to understand why there are such different percentages of LEAT subtypes in published surgical series, which some authors refer to as "geographical differences" (*see review of* Thom *et al.,* 2012). The majority of publications on epilepsy-associated brain tumours specify GGs as the most frequent tumour type, followed by DNTs and PAs (Khajavi *et al.,* 1999; Luyken *et al.,* 2003; Zaatreh *et al.,* 2003; Brainer-Lima *et al.,* 2006; Schramm and Aliashkevich, 2007; Sugano *et al.,* 2007; Ruban *et al.,* 2009; Prayson, 2010; Garcia-Fernandez *et al.,* 2011; Babini *et al.,* 2013; Cossu *et al.,* 2013; Rydenhag *et al.,* 2013; Fallah *et al.,* 2015; Bonney *et al.,* 2015, 2016). However, even in large series, the frequency of GGs can

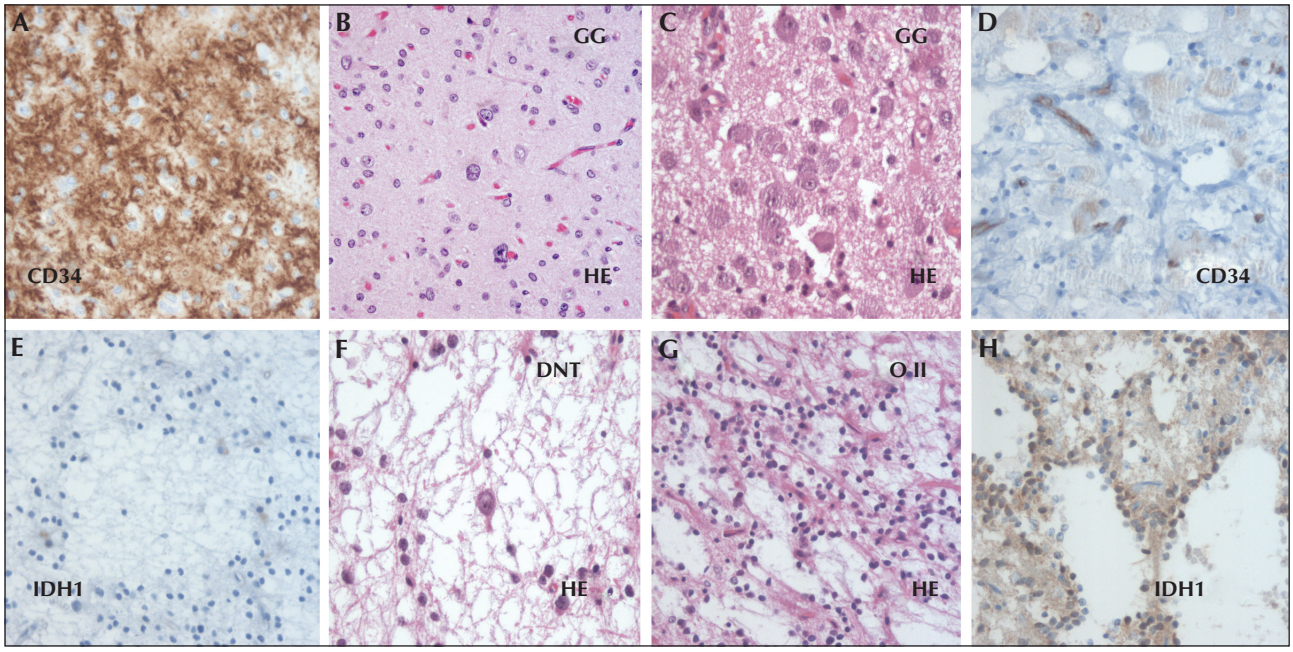

Figure 1. Histopathological challenges in the diagnosis of LEATs. Upper row shows two ganglioglioma variants. Compared to variant 2 (C-D), variant 1 (A, B) did not reveal any significant neuronal component on high magnification H&E (haematoxylin and eosin) staining (A), and one may argue that neurons are over-run by neoplastic glial cells. However, there is significant CD34 immunoreactivity (brownish colour in [A]), as well as dysplastic neurons in other areas of this specimen (not shown). The lower row demonstrates two tumours with an oligodendroglial (clear) cell component; microscopic inspection on H&E staining can be challenging. DNT WHO grade I (E-F) without *IDH1* mutation. Oligodendroglioma WHO grade II (OII) (G-H) with *IDH1* mutation.

vary from 6% to 49%, and for DNTs from even 7% to 80% (Thom *et al.*, 2012). It is very unlikely that different "geographies" provoke such differences, and there is reason to assume that agreement on histological criteria for the classification of benign brain tumours is not good enough among neuropathologists; *i.e.* a tumour classified as a DNT at one centre might be classified as a GG or low-grade astrocytoma at another centre. Currently, four different subtypes of DNTs have even been proposed in the literature: *simple*, *complex, diffuse*, and *non-specific* DNTs (Daumas-Duport, 1993; Daumas-Duport *et al.*, 1988, 1999; Honavar *et al.*, 1999; Thom *et al.*, 2011; Bodi *et al.*, 2012). Yet, differentiation between the four subtypes is not approved by the WHO, which recognises only *simple* and *complex* forms. The four subtypes are not different with respect to their biological behaviour (Thom *et al.*, 2011; Campos *et al.*, 2009; Chassoux *et al.*, 2013; Chassoux and Daumas-Duport, 2013), but may differ with respect to MRI signatures and the delineation of the epileptogenic zone (Chassoux *et al.*, 2013).

Another difficulty in classifying LEATs results from the variable histology (Daumas-Duport *et al.*, 1999; Blümcke and Wiestler, 2002; Thom *et al.*, 2011, 2012; Prayson and Napekoski, 2012; Blümcke *et al.*, 2014; Keser *et al.*, 2014). In one and the same glio-neuronal tumour entities, the relative proportion of glial cells and neurons can be very different from one tumour area to another (*figure 1*). Moreover, significant expertise is needed to judge the different neuronal and glial elements by microscopic inspection, *i.e.* whether a neuron is pre-existent and over-run by infiltrating glia or *bona fide* dysplastic. The variation of histological findings in GGs has been described in detail by Blümcke and Wiestler (2002). The "heterogeneous appearance" of glial elements in GGs sometimes resembles features of low-grade WHO II gliomas (Japp *et al.*, 2013). It was mentioned in the publication by Luyken *et al.* (2003) that in their large group of 184 GGs, 50 tumours were previously classified either as PAs, DAs, or GGs. In 18 of 129 tumours in the setting of paediatric chronic epilepsy at the Cleveland Clinic, a "distinction between low-grade glioma and low-grade glio-neuronal tumours could not be definitely made" (Prayson, 2010). One tumour was also referred to as "composite GG/DNT" (Prayson and Napekoski, 2012). "Tumours with features of DNT, but including aggregates of atypical neurons" were grouped by Thom *et al.* (2011) as "mixed GGs/DNTs" and the authors claim that "shared immuno-histochemical expression patterns support a GG/DNT glio-neuronal tumour spectrum". Our illustrative case report below is another example of a tumour with such challenging mixed histopathological features, which often irritates neuropathologists with only little experience in

epilepsy surgery. Other examples of "mixed LEATs" are tumours with elements of DNTs plus elements of PAs, and GGs plus pleomorphic xanthoastrocytoma (PXA) cell elements (review in Thom *et al.* [2012]). For tumours which do not meet typical criteria for WHO categories or have overlapping histology for multiple categories, the term "low-grade glioma not otherwise specified" (LGG-NOS) was introduced (Bergthold *et al.,* 2014). According to the "Central Brain Tumour Registry of the United States" (CBTRUS), this category comprises more than one third of all paediatric low-grade gliomas (PLGGs) (Dolecek *et al.,* 2012). However, this figure applies to all PLGGs. Yet, based on our own experience, as well as the literature, the percentage of LGG-NOS is much lower.

A third reason why a neuropathologist may not be able to classify or may misclassify a tumour can arise in a situation when only a fragment of the tumour is available for neuro-pathological investigation, *e.g.* a fragment containing just one of the pathological cell elements of this tumour type (Louis *et al.,* 2007b; Prayson, 2010). PGNTs, RGNTs, GNTNIs, and angiocentric gliomas may not always be classified correctly because they are so rare and have been described only recently (Li *et al.,* 2014).

Of more concern - different grading of one and the same LEAT

Uncertainty is not only restricted to histological classification but also to tumour grading (Daumas-Duport *et al.,* 1999; Campos *et al.,* 2009; Dozza *et al.,* 2012; Chassoux *et al.,* 2013). Some clinicians may consider discrepancies in the classification of benign brain tumours as an academic issue. Since tumour grading is likely to be also affected by diagnostic uncertainty, this issue should be discussed more carefully. Interestingly, misclassifications of benign tumours (by less experienced centres) seem to more often lead to an erroneous higher grading of the tumours, rather than the other way around (Campos *et al.,* 2009). The inter-observer agreement on histological features was poor for "institutionally (outside) diagnosed high-grade gliomas"; of 250 children who were enrolled in a trial to study the efficacy of radiotherapy, in addition to chemotherapy, 70 tumours (28%!) were re-classified as low-grade tumours according to a "*central review*" by a consensus of three out of five neuropathologists on *post hoc* evaluation (Fouladi *et al.,* 2003). A further analysis revealed that the overall survival rate (OSR) of these 70 children, who were treated with chemotherapy and radiotherapy, was not different from children with low-grade gliomas "who were treated with contemporary chemotherapy-alone approaches"! (Fouladi *et al.,* 2003). These observations are alarming considering the vulnerability of the young brain to radiotherapy and the risks of chemotherapy (*see illustrative case*).

Impact of neuropathological classification on patient management in a child with tumour-associated early epilepsy onset (an illustrative case report)

We report a young male child with seizure onset at age 13 months. His daily seizures consisted of falls and loss of consciousness. MRI at age 14 months revealed a left frontal lesion, leading to a suspicion of astrocytoma. A stereotactic tumour biopsy was performed at a local hospital and neuropathological diagnosis was determined as astrocytoma WHO grade II. Tumour surgery at the local hospital, with incomplete resection of the lesion (*figure 2A, C*), was carried out at age 15 months following a relapse of seizures after a seizure-free interval of four weeks on oxcarbacepine monotherapy.

Histopathological classification of the resected tumour specimen at the local hospital was anaplastic astrocytoma (WHO grade III; *figure 3A-C*). According to the HIT-HGG protocol of the German Society for Pediatric Oncology and Hematology, the patient underwent intensive chemotherapy instead of the combination of chemotherapy and radiation therapy. No growth of the remaining tumour mass was observed on close follow-up investigations, however, the last element of the protocol was not administered because of severe adverse effects.

The patient was referred to the epilepsy centre in Vogtareuth (Germany) at age 4 and a half years for presurgical evaluation. There was concern that relapse after several months of seizure freedom could be the result of tumour recurrence despite lack of MRI-visible tumour recurrence.

High-resolution MRI (1-mm slices), including gadolinium application, at our institution did not confirm any tumour progression. Furthermore, re-inspection of previous MRI revealed FLAIR signals and contrast enhancement, unusual for anaplastic astrocytoma grade III. A second look at the surgical specimen was initiated at the Germany Neuropathology Reference Center for Epilepsy Surgery in Erlangen (Germany) and classified as diffuse astrocytoma (WHO grade II; *figure 3A-C*). However, there was also a cautionary note with regards to sampling difficulties as only one of the four paraffin blocs of the original specimen was available for re-evaluation.

Repeat surgery was carried out at age 6 years, following invasive recording with subdural grids, subdural strips,

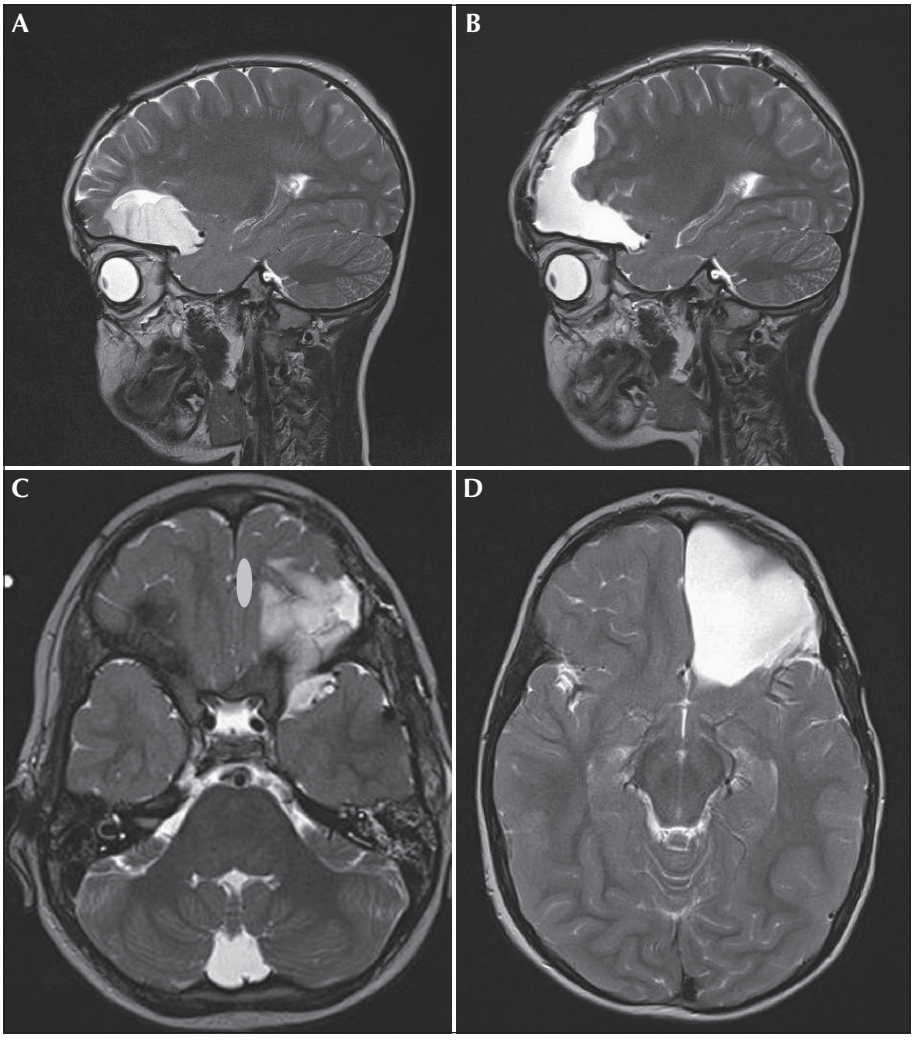

Figure 2. Post-surgical MRI following tumour vs. epilepsy surgery. (A, C) MRI 40 months after first surgery (at age 14 months). (B ,D) MRI after repeat surgery at age 6 years. The red dot in (C) indicates seizure onset recorded from subdural grids, strips, and depth electrodes. Broca's area could not be determined by direct electrical cortical stimulation, however, based on the result of invasive recording, a resection of the pars triangularis and pars opercularis frontalis was not necessary. Courtesy of P. Winkler, Olga Hospital Stuttgart & Neuropediatric Clinic and Clinic for Neurorehabilitation, Epilepsy Center for Children and Adolescence, Schoen-Kliniken Vogtareuth, Germany.

and three depth electrodes. A complete resection of the residual tumour mass and the epileptogenic zone was achieved (*figure 2B, 2C*). Histopathological classification of the second tumour specimen revealed a composite glio-neuronal tumour (GG and DNT) with features of atypia. This difficult classification summarised the many histological aspects of the tumour, including nodular growth with oligodendroglial-like cells and floating neurons (*figure 3D*), diffuse infiltration of astroglial cells (*figure 3E*), clusters of dysplastic neurons in an astroglial matrix (*figure 3F*), an increased proliferation index in the range of 6% (*figure 3J*), variable MAP2 staining in the glial component (*figure 3G, H*), no CD34 immunoreactivity, and no immunoreactivity to mutation-specific IDH1 antibodies.

The patient was completely seizure-free following the second operation (with a follow-up period of four years) and did not receive any further adjuvant tumour therapy. To date, there is no visible tumour recurrence on sequential MRI.

New insights into the biology of LEATs: immunohistochemical and molecular genetic testing will lead to changes in classification and patient management

The WHO classification of brain tumours from 1979 to 2007 was based on histological criteria with

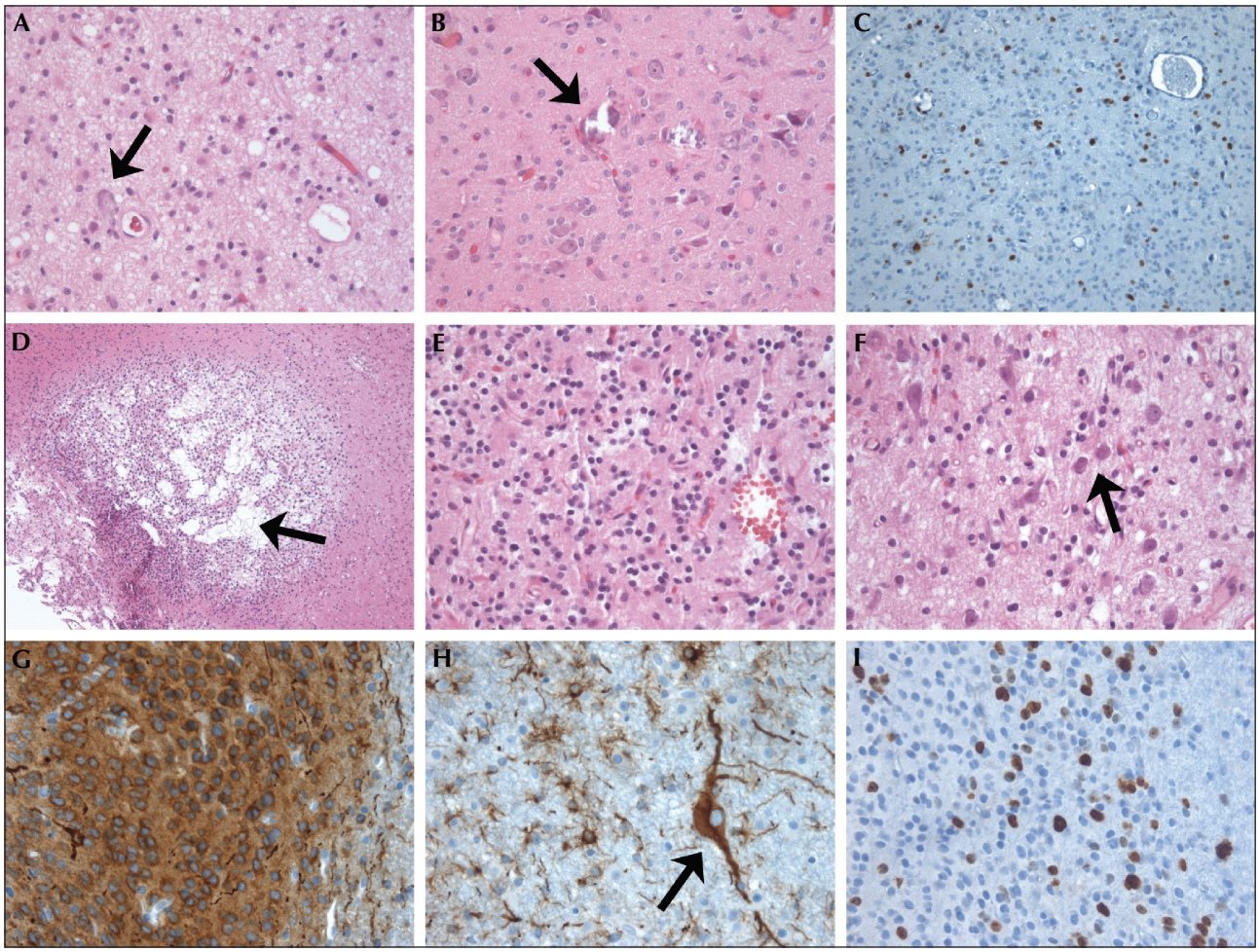

Figure 3. Variable microscopic appearance at the first and second operation. (A-C) Surgical specimen from first operation (diagnosis: anaplastic astrocytroma). (A) Diffusely infiltrating tumour of moderate cellularity in a glial matrix and with few large neurons (arrow). (B) Neocortical infiltration of tumour cells; arrow points to a small amount of calcification. (C) Area of tumour with maximum proliferation (approx. 5%). No further staining for CD34, MAP2, or IDH1 were available at the local hospital. (D-I) Surgical specimen from the second operation (histopathological diagnosis: composite glio-neuronal tumour with atypical features (analogue WHO grade II). (D) Nodular tumour growth (arrow) with characteristic features of a DNT. (E) Astroglial tumour component with moderate cellularity and increased proliferation activity (I). (F) Glio-neuronal component with clusters of dysplastic neurons (arrow), not otherwise explicable by anatomical features. MAP2 staining pattern was also variable in this tumour with densely immunoreactive tumour cells (G), compared to areas in which MAP2 was restricted to dysplastic neurons (arrow in [H]). H&E staining (A-B, D-F); proliferation marker Ki67 (C, I); MAP2 immunohistochemistry (G-H). Scale bar in (A)=50 μm, applies also to (B, E-I); scale bar in (C)=100 μm; scale bar in (D)=250 μm.

neuropathological investigations using conventional methods of microscopic inspection which should be available all over the world, *e.g.* haematoxylin and eosin staining, with or without additional immunostaining for glial fibrillary acidic protein (GFAP) or the neuronal marker for synaptic vesicles, *i.e.* synaptophysin. There is ongoing controversy regarding the fact that such a restricted panel will not be sufficient for the classification and grading of the large histomorphological spectrum of brain tumours. Because of shortcomings with conventional histological routine, neuropathologists and oncologists are continuously calling for advanced immunehistochemical and molecular genetic testing for LEATs (Korshunov *et al.*, 2009; Thom *et al.*, 2012; Schindler *et al.*, 2011; Rodriguez *et al.*, 2013; Blümcke *et al.*, 2014; Bergthold *et al.*, 2014; Blümcke *et al.*, 2016), *e.g.* immunostaining for the oncofoetal protein CD34 (present in 80% of GGs) (Blümcke *et al.*, 1999a, 1999b) and the microtubule-associated protein 2 (MAP2) (Blümcke *et al.*, 2001, 2004). These investigations ought to be supplemented by genetic testing for *fusions* and *mutations* of the proto-oncogene BRAF. BRAF fusions are found predominantly in PAs, but also in PXAs, GGs, and DNTs, whereas high-grade paediatric gliomas are not affected (Jones *et al.*, 2008). BRAF V600E mutations

are found in almost 100% of PXAs, in a high percentage of PAs, seldom in DAs, and to variable degrees in other LGGs and glio-neuronal tumours (Qaddoumi *et al.,* 2016). The implication of BRAF alterations in the classification of brain tumours, as well as their good predictive and prognostic value, are discussed in several reviews (Horbinski, 2013; Marko and Weil, 2013; Rodriguez *et al.,* 2013; Bergthold *et al.,* 2014; Penman *et al.,* 2015). BRAF alterations seem to be the most relevant molecular changes (Schindler *et al.,* 2011; Koelsche *et al.,* 2013; Prabowo *et al.,* 2014), but not the only ones (see CBTRUS website http:// www. cbtrus.org). Further insight into the nature of brain tumours was gained by testing for genomic alterations, *e.g.* impaired function of isocytrate dehydrogenase (IDHI1 and IDH2), which was found to be mutated in up to 90% of mixed grade II and III gliomas/oligodendrogliomas/gliomas in adults (Capper *et al.,* 2010, 2011), but far less so in children and primary high-grade gliomas (glioblastomas), and either not or very rarely mutated in GGs and DNTs (Sturm *et al.,* 2012; Marko and Weil, 2013; Rodriguez *et al.,* 2013). Further testing for chromosomal aberrations is highly recommended for all diffusely infiltrating gliomas that are WHO grade II or higher, *e.g.* co-deletion of chromosomal arms 1p and 19q is not only a predictive marker for oligodendrogliomas and oligoastrocytomas (WHO grade II and III), but also useful for determining prognosis in patients with tumours carrying a 1p/19q co-deletion (Jenkins *et al.,* 2006).

In preparation for the revision of the 2016 WHO classification, the International Society of Neuropathology (ISN) published guidelines and algorithms on how "molecular information" should be incorporated in new classification systems (Louis *et al.,* 2014, 2016a). Appropriate use of these new diagnostic tools will increase the predictive yield of specific tumour diagnosis and thereby reduce the number of patients who are unnecessarily treated with chemotherapy and/or radiotherapy. Routine application of such tests would most likely identify more patients and would reveal earlier, who is at risk of malignant tumour progression and needs to be followed under oncological surveillance (Thom *et al.,* 2012; Japp *et al.,* 2013; Ostrom *et al.,* 2013; Blümcke *et al.,* 2014). Available molecular genetic data have been gathered and validated by a large number of prospectively randomised clinical trials for diffusely infiltrating and high-grade gliomas (Wick *et al.,* 2009; Laperriere *et al.,* 2013; Weller *et al.,* 2015). However, there is a lack of similar trials in the area of epilepsy surgery and LEATs. Therefore, validation of new diagnostic avenues for LEATs towards better diagnosis, determining the extent of the epileptogenic zone, and long-term prognoses remains to be demonstrated. This requires prospective multicentre studies within the epilepsy community, which could provide a database for such rational management. An important question is whether it is possible to predict that a child's LEAT is curable by resection or whether it requires regular surveillance due to a less favourable prognosis.

Finally, epileptologists should be aware of the fact that upcoming biomarkers, such as BRAF alterations, *IDH1*/*IDH2* mutations, *MGMT* promoter methylation, and 1p/19q co-deletions, will be important with regards to choosing a *targeted* immunotherapy, chemotherapy and/or radiotherapy in selected cases in which such therapies are available and their benefit is confirmed in prospectively randomised clinical trials. Indeed, the fourth edition of the WHO classification of tumours of the central nervous system has been published during the review process of this manuscript (Louis *et al.,* 2016b). An integrated phenotypic-genotypic diagnosis will now be requested for many tumours, such as diffuse gliomas and embryonal tumours (Louis *et al.,* 2016a). In contrast, the WHO panel of experts could not agree on significant changes for LEATs. Reasons for this lack of innovation are multi-layered, as extensively discussed above (*e.g.* published studies on the molecular-genetic characterisation of LEATs are difficult to compare, as different histopathological classification schemes have been applied; no randomised clinical trials were available to verify clinically meaningful LEAT entities or subtypes).

Huge variation in associated focal cortical dysplasias in published series of patients with LEATs

Finally, we wish to address another issue of ongoing controversial discussion amongst neuropathologists and epileptologists. How can we explain the huge variation regarding the frequency of focal cortical dysplasia (FCD) in association with benign brain tumours, ranging from 0 up to 80%, reported in different studies (*see table 1 from a recent review of surgical DNT series*) (Bonney *et al.,* 2016)?

The most likely explanation for these astonishing discrepancies is the fact that one neuropathologist will judge an area with abnormal cortical architecture outside the bulk tumour as FCD, whereas another colleague will use immunohistochemistry (*e.g.* CD34, NeuN, SMI32, and MAP2) to exclude remote LEAT tumour cell infiltration or the presence of small LEAT satellite clusters, which have been well described in GGs and DNTs (Thom *et al.,* 2012; Blümcke and Wiestler, 2002). If an FCD is unambiguously identified (usually cortical dyslamination and hypoplasia), it should be classified as FCD type IIIb, according to the ILAE classification of FCDs (Blümcke *et al.,* 2011). This specific terminology allows *bona fide* FCD I and II to be considered apart, and enables further

assessment of any specific underlying pathogenesis by applying advanced comparative molecular and neurophysiological studies in well diagnosed groups of patients. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) Which tumours are often associated with "long-term and drug-resistant epilepsy"?
A. Ganglioglioma
B. Glioblastoma
C. Anaplastic astrocytoma
D. Dysembryoblastic neuroepithelial tumour
E. Papillary glio-neuronal tumour
F. Medulloblastoma
G. Angiocentric glioma
H. Schwannoma

(2) Why is the histopathological classification of a LEAT difficult?
(i) Biphasic glio-neuronal patterns can be similar in different LEATs.
(ii) Lack of molecular-genetic biomarkers requires significant experience in microscopic inspection and differentiation of neuronal and glial cell elements.
(iii) Neuropathologists may not be provided with enough material for diagnostic work-up, *e.g.* when surgery is performed in the dominant hemisphere or close to eloquent brain regions.
A. Only (i) is correct
B. (i) and (ii) are correct
C. All three are correct

(3) What is the most frequent brain localization for "long-term epilepsy associated tumours" (LEATs)?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".