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LETTER TO THE EDITOR

Challenges in epilepsy-associated tumors

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To the Editor,

Epilepsy-associated tumors (EATs) encompass a large spectrum of low-grade glial or glioneuronal tumors frequently encountered in epilepsy surgery practice. EATs are currently a common cause of focal epilepsy, especially in children and young adults, with epilepsy as the primary and almost always dominant symptom [1–7].

For this group of tumors the acronym "LEATs" (long-term epilepsy associated tumors) [1, 3] has been proposed. By definition, the adjective "long term" means that drug-resistant seizures occur for 2 years or more.

Glioneuronal tumors and focal cortical dysplasia (FCD) often coexist and their specific roles in epileptogenesis is still not well defined [3–6, 8].

The most recent internationally adopted FCD classification (8) identifies the group of FCD type IIIb (including cortical lamination abnormalities, FCD type I) adjacent to a glial or glioneuronal tumor. However, when glioneural tumors are associated with FCD type II, characterized by large and dysmorphic neurons with or without the presence of balloon cells [4, 6], the ILAE Classification suggests to consider them as a double pathology [8].

The new FCD type IIIb class [8] could produce confusion about the oncological follow-up and management of patients.

Considering that these tumors need to be followed up also for epilepsy, the summarized format of histological diagnosis of FCD type IIIb may be misleading in clinical practice, shifting the focus to the non-progressing part (FCD) of this compound disease.

Therefore, this condensed label may induce the epilepsy surgery team to neglect the most appropriate oncological follow-up.

Unlike the other FCD type III (a, c, d) in which the principal lesion has no "progressing potential" (hippocampal sclerosi (HS), vascular malformations, ischemic or trauma injury, encephalitis) [8] in FCD type IIIb the principal lesion is a low-grade tumor that requires a different clinical and imaging follow-up, involving neurologists, neurosurgeons and neurooncologists.

In our opinion the current definition of FCD type IIIb is unsatisfactory because it puts emphasis on the FCD and may cause the underestimation of the tumor's behavior and aggressiveness.

In fact, the spectrum of EATs involves an increasingly wide variety of lesions, e.g. glioneuronal tumors (gangliglioma (GG), dysembryoplastic neuroepithelial tumors (dnet), papillary glioneuronal tumor) and glial tumors (pilocytic astrocytoma, pleomorphic xanthoastrocytoma–(PXA), diffuse astrocytoma, oligodendroglioma, angiocentric glioma) [1, 3, 9]. Furthermore, compound EATs (i.e., GG+PXA, GG+Dnet) have been reported [10].

The biological behavior of these tumors is not completely understood, but it is well known that tumors like PXA or diffuse gliomas tend to recur and may become high-grade gliomas. Recently, the knowledge about molecular features of EATs has rapidly grown [3, 5, 9, 11] and, at the same time, the molecular alterations that characterize diffuse gliomas [9, 12] have been recognized as important diagnostic, prognostic and predictive factors.

An essential task would be the identification of those tumors with a higher propensity for recurrence or even malignant progression, and also the characterization of

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molecular features associated with risk of recurrence and anaplastic progression may be very helpful.

The increasing knowledge of molecular aspects of EATs may allow more precise histological definition and a better comprehension of oncological behaviour. This is particularly important because these lesions are now usually well recognized and early operated on, and a long-term epilepsy history (that in the past actively contribute to characterize these lesions) is more and more frequently absent. For example, there is already significant evidence that brain somatic activating mutations in mTOR are associated with different epileptogenic conditions under the term of 'mTORopathies', such as tuberous sclerosis, FCD, hemimegalencephaly and ganglioglioma [13, 14].

For all these reasons, we suggest classifying the association between EATs and FCD as a double pathology, providing the appropriate evidence for the tumor histotype and the FCD type.

Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to disclose.

References

1. 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(6):822–830
2. Blümcke I, Spreafico R (2012) Cause matters: A neuropathological challenge to human epilepsies. Brain Pathol 22(3):347–349
3. Thom M, Blümcke I, Aronica E (2012) Long-term epilepsy-associated tumors. Brain Pathol 22:350–379
4. Giulioni M, Marucci G, Martinoni M, Volpi L, Riguzzi P, Marliani AF, Bisulli F, Tinuper P, Tassinari CA, Michelucci R, Rubboli G (2013) Seizure outcome in surgically treated drug-resistant mesial temporal lobe epilepsy based on the recent histopathological classifications. J Neurosurg 119(1):37–47. doi:10.3171/2013.3.JNS122132
5. Japp A, Gielen GH, Becker AJ (2013) Recent aspects of classification and epidemiology of epilepsy-associated tumors. Epilepsia 54:5–11
6. Cossu M, Fuschillo D, Bramerio M, Galli C, Gozzo F, Pelliccia V, Casaceli G, Tassi L, Lo Russo G (2013) Epilepsy surgery of focal cortical dysplasia-associated tumors. Epilepsia 54 (Suppl 9): 115–122. doi:10.1111/epi.12455
7. Englot DJ, Chang EF (2014) Rates and predictors of seizure freedom in resective epilepsy surgery: an update. Neurosurg Rev 37(3):389–404. doi:10.1007/s10143-014-0527-9 (**discussion 404–405**)
8. 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
9. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 world health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. doi:10.1007/s00401-016-1545-1
10. Prayson RA, Napekoski KM (2012) Composite ganglioglioma/dysembryoplastic neuroepithelial tumor: a clinicopathologic study of 8 cases. Hum Pathol 43:1113–1118
11. Marucci G, de Biase D, VisaniM, GiulioniM, MartinoniM, Volpi L, Riguzzi P, Rubboli G, Michelucci R, Tallini G (2014) Mutant BRAF in low grade epilepsy-associated tumors and focal cortical dysplasia. Ann Clin Transl Neurol 1(2):130–134. doi:10.1002/acn3.31
12. Cancer Genome Atlas Research Network (2015) Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 372:2481–2498
13. Liu J, Reeves C, Michalak Z, Coppola A, Diehl B, Sisodiya SM, Thom M (2014) Evidence for mTOR pathway activation in a spectrum of epilepsy-associated pathologies. Acta Neuropathol Commun 8(2):71. doi:10.1186/2051-5960-2-71
14. Lim JS, Kim WI, Kang HC, Kim SH, Park AH, Park EK, Cho YW, Kim S, Kim HM, Kim JA, Kim J, Rhee H, Kang SG, Kim HD, Kim D, Kim DS, Lee JH (2015) Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. Nat Med 21:395–400