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The etiopathogenesis of diffuse low-grade gliomas

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ABSTRACT

The origins of diffuse low-grade gliomas (DLGG) are unknown. Beyond some limited data on their temporal and cellular origins, the mechanisms and risk factors involved are poorly known. First, based on strong relationships between DLGG development and the eloquence of brain regions frequently invaded by these tumors, we propose a "functional theory" to explain the origin of DLGG. Second, the biological pathways involved in DLGG genesis may differ according to tumor location (anatomo-molecular correlations). The cellular and molecular mechanisms of such "molecular theory" will be reviewed. Third, the geographical distribution of diffuse WHO grade II–III gliomas within populations is heterogeneous, suggesting possible environmental risk factors. We will discuss this "environmental theory". Finally, we will summarize the current knowledge on genetic susceptibility in gliomas ("genetic predisposition theory").

These crucial issues illustrate the close relationships between the pathophysiology of gliomagenesis, the anatomo-functional organization of the brain, and personalized management of DLGG patients.

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1. Introduction

To date, the origins and etiologic factors of diffuse low-grade gliomas (DLGG) are mostly unknown. There is, however, a few data regarding their temporal origins. Indeed, because the DLGG growth rate is constant during the initial premalignant symptomatic period, it was possible to extrapolate backwards in time, leading to the approximate glioma date of birth in early adulthood (around 20 years of age) (Mandonnet et al., 2003; Duffau et al., 2011; Gerin et al., 2012). This suggests that DLGG arise more likely "ex nihilo" rather than from a preexisting congenital lesion.

Although the causative factors of DLGG are poorly known, it is already noteworthy to mention that the implication of one unique etiologic factor for all DLGG is unlikely, as these tumors represent a heterogeneous entity. Indeed, recent refinement of the biomathematical model, based on a differential equation describing the diffusion–proliferation process, has enabled the identification of two types of DLGG: firstly, very slow-growing tumors that appear during adolescence; secondly, slow-growing tumors that appear later during the young adult period (Gerin et al., 2012). These different DLGG subgroups attest of the heterogeneity among DLGG and of the complexity of DLGG genesis.

The aim of this article is to review the possible mechanisms underlying the genesis of DLGG. One way to better understand these mechanisms is to study their spatial distribution, both within the brain and at the geographical level within populations (at the international and national levels), as some hypothesis regarding the mechanisms may be speculated from these distributions.

Indeed, DLGG have preferential locations within the brain, mostly within the so-called "functional areas", and these locations are different from that of other gliomas (including glioblastomas) (Duffau and Capelle, 2004). This observation leads to consider two hypotheses regarding the DLGG genesis. First, it is possible that the brain microenvironment, shaped by environmental demands and specific regional neuron-microenvironment interactions, might influence the risk of tumor development (" the functional theory"). Second, it can be hypothesized that the biological pathways involved in the DLGG genesis may differ according to the tumor location. Biological differences according to the tumor location have been demonstrated ("the molecular theory"), including for example the mutation of the isocitrate dehydrogenase (IDH) gene that is considered as an early event in the DLGG genesis. We will review the current knowledge on the cellular and molecular origins of DLGG.

Moreover, the geographical distribution of lower-grade gliomas (World Health Organization or WHO diffuse grade II and grade III gliomas) is also heterogeneous. This has been recently demonstrated by our team in a study of 4790 patients with a newly diagnosed, histologically-proven lower-grade glioma (WHO 2007 classification) in metropolitan France (Darlix et al., 2014). This observation raises the question of the role of environmental risk(s) factor(s) ("the environmental theory"), which will also be addressed in this article.

Finally, we will briefly summarize the current knowledge on genetic susceptibility in gliomas.

2. DLGG have preferential brain locations

DLGG have preferential locations within the brain (Duffau and Capelle, 2004; Capelle et al., 2013; Parisot et al., 2016). These locations have been reported using various methods: the classical methods based on the lobar anatomy, the voxel-wise methods, and the probabilistic approaches.

At the lobar level, a first report showed a frequent involvement of so-called "functional" areas, namely the supplementary motor area (SMA) (27.3%) and the insula (25%), with a significant difference when compared with *de novo* glioblastomas, suggesting a possible different origin between these two kinds of gliomas (Duffau and Capelle, 2004). This preliminary observation was confirmed by a study demonstrating a higher rate of DLGG in anterior regions of the brain (Laigle-Donadey et al., 2004), and then by a French study on a large 1097 DLGG series in which about 90% of patients had a tumor located in the frontal and/or-temporal and/or-insular regions (Capelle et al., 2013). More recently, in a series of 198 DLGG patients from our team, the tumor distribution was as follows: 31.3% frontal, 23.7% temporo-insular, 20.2% fronto-temporo-insular, 12.1% parietal, 9.1% fronto-insular and 3.5% of other locations.

However, these DLGG spatial classifications based on cerebral lobe or gyri lack accuracy. More recently, two other new approaches, a voxel-wise method and a probabilistic approach, have confirmed this data. Our team used, for the first time, a voxel-wise method to assess the intra-cerebral topography of 198 DLGG patients at diagnosis. As illustrated in Fig. 1, the overlap map of all 198 tumors showed a quite homogeneous and symmetrical distribution of the tumors within the fronto-temporo-insular regions (unpublished data).

The other approach consists in the construction, by means of a novel probabilistic method, of a graph-based spatial position mapping (Parisot et al., 2016, 2011). We applied this methodology in a consecutive series of 210 DLGG patients at diagnosis, and confirmed the symmetrical distribution of the tumors and the preferential location within frontal (33%), insular (37%) and temporal (18%) areas (Fig. 2).

Whatever the methodology used to assess the preferential locations for DLGG, two main findings should be highlighted. On one hand, DLGG are preferentially located within the so-called "eloquent" areas, including the insula and the SMA, which are both functional interfaces between the limbic system (mesiotemporal structure and cingulum) and the temporal pole (for the insula) or the prefrontal cortex (for the SMA). On the other hand, there are very few DLGG located in the posterior regions of the brain, including the occipital lobe. In a large consecutive series of DLGG recently reported by the UCSF team, only two out of 281 patients (0.71%) had an occipital tumor involving visual regions (Chang et al., 2011). Similarly, in the French Low-Grade Gliomas Consortium series, only 5 out of 1094 (0.46%) DLGG were occipital (Capelle et al., 2013). The results are almost similar in our consecutive experience with about 400 DLGG, since only six patients (2.0%) had an occipital glioma (Viegas et al., 2011). These findings lead to several biological hypotheses regarding DLGG genesis. First, the cytoarchitectony of the visual cortex is not the same, since the insula is constituted by a mesocortex, making a link between the allocortex and the neocortex (Duffau and Capelle, 2004). Second, from a functional point of view, both the insula and the SMA play a role in the planning of movements and language (Duffau, 2009a; Krainik et al., 2003), while the occipital lobe is not involved in planning. It can thus be hypothesized that the risk of DLGG is linked, among other factors, to the eloquence of the area involved and that there may be an impact of the microenvironment on DLGG development ("the functional theory"). Another hypothesis is that differences linked to developmental processes, including the myelination processes, could be involved. Indeed, fronto-temporal areas are among the last myelinated areas during development, the myelination processes occurring until the second decade of life, particularly in the frontal lobe (Paus et al., 1999). In the study published by Paus et al. in 111 children and teenagers (4–17 years old), there was an age-dependent increase in white matter density in several areas including the posterior part of the arcuate fasciculus connecting the frontal and temporal areas and involved in language (Paus et al., 1999). Interestingly, the myelination processes seem

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