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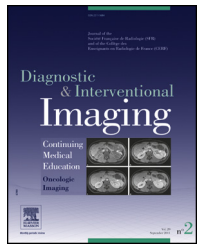

CONTINUING EDUCATION PROGRAM: FOCUS...

Diffuse low-grade gliomas and neuroplasticity

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Abstract The traditional approach in neuro-oncology is to study the tumor in great detail and ultimately give little consideration to the brain itself. Choosing the best treatment strategy for each patient with a diffuse low-grade glioma, in other words optimizing the oncologic and functional balance, implies not only a full knowledge of the natural history of this chronic disease, but also an understanding of the adaptation of the brain in response to growth and spread of the glioma. The aim of this review is to examine the mechanisms underlying this neuroplasticity, allowing functional compensation when the tumor progresses, and opening the way to new treatments with the principle of shifting towards ''functional personalized neuro-oncology'', improving both median survival and quality of life.

The traditional approach in neuro-oncology is to study the tumor extensively and ultimately with little consideration given to the brain itself. It is however crucial to take account of the ''onco-functional balance'', i.e. to find the optimal ratio both in terms of the tumor and quality of life to decide on a suitable treatment strategy, particularly in patients with diffuse low-grade gliomas (DLGG) [1]. In this context, whilst understanding the natural history of this chronic tumor is obviously essential, it is however not sufficient. It is also essential to study the reaction of the central nervous system which is induced by the growth and migration of the glioma. In other words because of the close relationships between the tumor and the brain, the brain may adopt adaptatory mechanisms to compensate for the spread of neoplastic cells [2].

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The aim of this review is to examine these neuroplasticity effects in order to move towards individualized treatment based on the dynamic interactions between DLGG and functional reorganization of the brain in order to improve both median survival and the patient's quality of life.

From localizationism to the connectome

On the basis of phrenologic theories, the localizationist view of the functioning of the central nervous system has been the approach used for over a century. By this principle, each region of the brain corresponds to a given function, and a lesion in an ''eloquent'' area is therefore presumed to result in a massive and permanent neurological deficit. In reality, because of the many observations of recovery after brain damage, including damage to areas deemed to be ''functional'' by the conventional approach, the concept of a rigid modular organization of the brain has been questioned, moving towards a connectionist philosophy. In this model, the central nervous system is organized into parallel networks, which are dynamic, interactive and able to compensate for each other - at least to a certain extent [3]. This goes back to a hodotopic principle, through which the functions of the brain are supported by extensive circuits comprising both the cortical epicenters (topos, i.e. sites) and connections between these ''nodes'', created by associating bundles of white matter (hodos, i.e. pathways) [4]. Neurological function comes from the synchronization between different epicenters, working in phase during a given task, and explaining why the same node may take part in several functions depending on the other cortical areas with which it is temporarily connected at any one time. In this context, functional maps may be reorganized within remote networks, making neuroplasticity mechanisms possible, both physiologically (ontogenics and learning) and after brain injury [5,6].

The potential of this post-damage plasticity however has been shown to correlate directly with the temporal pattern of the neurological damage. Whilst only modest redistribution of neurosynaptic networks occurs in acute injury such as stroke, explaining the limited recovery in many patients, massive redistribution occurs in chronic slowly progressive injuries, particularly in DLGG, explaining why patients generally develop few if any deficits [7]. Furthermore, a probabilist atlas designed to study the plasticity index depending on tumor site has recently been reported [8] and shows that whilst the potential for cortical reorganization is considerable, it is very limited in terms of subcortical connectivity. In other words, it is crucial to preserve the connectome in order to achieve functional compensation after a cerebral injury. This is a very important concept in the treatment of patients with DLGG, particularly with respect to surgery [9].

Natural history of DLGG, neuroplasticity and functional state

DLGG is a rare primary brain tumor (with an incidence in about 1/100,000 people annually), which generally presents as an epileptic seizure (and occasionally incidentally) in young adults with an active family, social and occupational life [1]. Unlike claims made for decades, these lesions progress slowly but constantly. Examination of the tumor growth curve by comparing its mean diameter

(calculated from its volume from the equation:

$$d = \sqrt[3]{\frac{6Vol}{\pi}}$$

on two MRIs 6 weeks to 3 months apart before any treatment has shown linear radiological growth in mean diameter of approximately 4 mm per year [10]. As a result, the concept of ''progression-free survival'' has no meaning in untreated DLGG or following incomplete surgical excision, as by definition all DLGG progress continually (except after complete excision or if it stabilizes as a result of chemotherapy or radiotherapy). In this context, the conventional radiological criteria initially proposed by McDonald, or more recently by the RANO group [11], are not appropriate for DLGG, as they only take account of the calculation of two diameters and not of volume (from which however the mean diameter can be deduced secondarily, see above). In addition, these tumors spread along the white matter bundles and inevitably transform into malignant gliomas—which influences both functional prognosis and survival, as median survival is in about 6 years if only a diagnostic biopsy is taken after radiological diagnosis [12].

On one hand, the very gradual growth of the tumor over the years leaves the central nervous system time to reorganize itself as the tumor infiltrates. For this reason, a standard neurological examination at the time of diagnosis is usually normal, despite DLGG frequently being located in regions conventionally deemed to be ''eloquent'' (for example, the supplementary motor area, insula, Broca's area or the central area) [13].

On the other hand, extensive neuropsychological assessments have shown that cognitive disorders are very common, although have long been underestimated. Whereas these patients were conventionally considered not to have any higher function deficit, many cognitive abnormalities have recently been found with repercussions on quality of life. These problems generally involve the attention processes, working memory, executive functions, learning, and even emotional or behavioral aspects, and have been found in almost 90% in patients before any treatment. These suggest that the DLGG itself has a negative impact [14]. In more specific terms, the deficits have been shown to be significantly related to infiltration of the subcortical association pathways and not to infiltration of specific cortical regions. Specifically, spread of the glioma along the left inferior fronto-occipital fascicle correlates with semantic processing disorders [15]. These results support the theories described previously of a hodotopic and not locationist organization of the central nervous system, in which the connectome represents the major limitation to plasticity mechanisms [3]. Routine neuropsychological assessments with quality of life assessment scales are now recommended in all patients with DLGG, as the standard neurological examination is ultimately too crude to be able to identify subtle deficits [16].