Diffuse low-grade glioma

Diffuse low-grade glioma (also often referred to as diffuse astrocytomas) are designated as WHO II tumours of the brain. The term diffuse infiltrating means there is no identifiable border between the tumor and the normal brain tissue even though the borders may appear well marginated on imaging.

Diffuse WHO Grade II glioma (diffuse low-grade glioma (DLGG) is an infiltrative brain tumor that usually migrates along the white matter tracts.

It is commonly believed that, before being diagnosed after onset of symptoms, diffuse low-grade glioma evolve silently for a long time.

First, glioma-initiating cells neoplastically transform, which we define as the biologic birth. This nascent glioma does not give rise to any symptoms and even remains below the detection limit of routine magnetic resonance imaging (MRI), during what we term the occult stage. Second, at some point, the glioma becomes visible on MRI, yet the patient is still asymptomatic; we refer to this as the clinically silent stage.

During this stage, gliomas can be incidentally discovered on brain MRI, for instance, in healthy volunteers from a study, in trauma patients requiring brain imaging, or in clients of commercial screening programs. Third, the glioma elicits clinical symptoms, usually an epileptic seizure, entering what we define as its symptomatic stage. Fourth, at some point in time, the glioma switches its rather indolent behavior toward an aggressive one, in keeping with the onset of neoangiogenesis and malignancy, until the patient dies from tumor spread and growth. To date, oncologic therapy has failed to cure patients with DLGG, but a significant delay of malignant transformation and death from disease can be achieved by appropriate and timely treatment [1)]

The delayed CSF dissemination of supratentorial DLGGs is an exceptional complication and is rarely described in adults.

Total or subtotal surgical resection can significantly increase survival. Moreover, a supratotal resection, i.e., an extended resection with a margin beyond MR imaging abnormalities, could decrease the risk of malignant transformation.

Guidelines

These recommendations apply to adult patients with recurrent low-grade glioma (LGG) with initial pathologic diagnosis of a WHO grade II infiltrative glioma (oligodendroglioma, astrocytoma, or oligo-astrocytoma). PATHOLOGY AT RECURRENCE:

QUESTION:

Do pathologic and molecular characteristics predict outcome/malignant transformation at recurrence? RECOMMENDATIONS:

IDH STATUS AND RECURRENCE: (Level III) IDH mutation status should be determined as LGGs with IDH mutations have a shortened time to recurrence. It is unclear whether knowledge of IDH mutation status provides benefit in predicting time to progression or overall survival. TP53 STATUS AND RECURRENCE: (Level III) TP53 mutations occur early in LGG pathogenesis, remain stable, and are not recommended as a marker of predisposition to malignant transformation at recurrence or other

measures of prognosis. MGMT STATUS AND RECURRENCE: (Level III) Assessment of MGMT status is recommended as an adjunct to assessing prognosis as LGGs with MGMT promoter methylation are associated with shorter PFS (in the absence of TMZ) and longer post-recurrence survival (in the presence of TMZ), ultimately producing similar overall survival to LGGs without MGMT methylation. The available retrospective reports are conflicting and comparisons between reports are limited CDK2NA STATUS AND RECURRENCE: (Level III) Assessment of CDK2NA status is recommended when possible as the loss of expression of the CDK2NA via either methylation or loss of chromosome 9p is associated with malignant progression of LGGs. PROLIFERATIVE INDEX AND RECURRENCE: (Level III) It is recommended that proliferative indices (MIB-1 or BUdR) be measured in LGGs as higher proliferation indices are associated with increased likelihood of recurrence and shorter progression free and overall survival. 1P/19Q STATUS AND RECURRENCE: There is insufficient evidence to make any recommendations. CHEMOTHERAPY AT RECURRENCE:

QUESTION:

What role does chemotherapy have in LGG recurrence? RECOMMENDATIONS:

TEMOZOLOMIDE AND RECURRENCE: (Level III) Temozolomide is recommended in the therapy of recurrent LGG as it may improve clinical symptoms. Oligodendrogliomas and tumors with 1p/19q co-deletion may derive the most benefit. PCV AND RECURRENCE: (Level III) PCV is recommended in the therapy of LGG at recurrence as it may improve clinical symptoms with the strongest evidence being for oligodendrogliomas. CARBOPLATIN AND RECURRENCE : (Level III) Carboplatin is not recommended as there is no significant benefit from carboplatin as single agent therapy for recurrent LGGs. OTHER TREATMENTS (NITROSUREAS, HYDROXYUREA/IMANITIB, IRINOTECAN, PACLITAXEL) AND RECURRENCE: There is insufficient evidence to make any recommendations. It is recommended that individuals with recurrent LGGs be enrolled in a properly designed clinical trial to assess these chemotherapeutic agents. RADIATION AT RECURRENCE:

QUESTION:

What role does radiation have in LGG recurrence? RECOMMENDATIONS:

RADIATION AT RECURRENCE WITH NO PREVIOUS IRRADIATION: (Level III) Radiation is recommended at recurrence if there was no previous radiation treatment. RE-IRRADIATION AT RECURRENCE: (Level III) It is recommended that re-irradiation be considered in the setting of LGG recurrence as it may provide benefit in disease control. SURGERY AT RECURRENCE:

There is insufficient evidence to make any specific recommendations. It is recommended that individuals with recurrent LGGs be enrolled in a properly designed clinical trial to assess the role of surgery at recurrence [2)]

Outcome

Diffuse low-grade glioma are radiologically detectable but clinically silent for more than a decade. Such a long period of silent evolution could explain our current failure to cure these tumors. It can also be viewed as a window of opportunity to detect these tumors earlier, suggesting the need to set up a screening program.

Despite advances in treatment, diffuse low-grade gliomas are still incurable. One reason for this might be the very long silent evolution of these tumors before clinical onset, estimated to last about 15 years [3)].

At detection, the microscopic infiltration, combined with genomic heterogeneity, which has accumulated over the years, makes it much harder to find a curative solution. The potential of early detection follows naturally, considering the emerging evidence that early treatment of incidental gliomas could improve the survival and quality of life [4].

Complications

Although rare, brain tumors, including low grade astrocytoma, should be considered a possible cause of subcortical hemorrhage in patients without risk factors for intracranial hemorrhage [5].

Case series

2015

Sixteen consecutive patients who underwent supratotal resection for a DLGG with a minimum follow-up of 8 years after surgery were included. The resection was continued up to functional cortical and subcortical structures defined by intrasurgical electrical mapping. The extent of resection was evaluated on postoperative FLAIR-weighted MR imaging. Data regarding clinicoradiological features, therapeutic management, and outcomes were analyzed.

Seven men and nine women (mean age, 41.3 years, range, 26-63 years) were included (seizure in 15 cases, one incidental discovery). All patients resumed a normal life after surgery (no neurological deficits, no epilepsy). The volume of postoperative cavity was larger than the preoperative tumor volume in the 16 patients. Neuropathological examination confirmed the diagnosis of WHO grade II glioma in all cases. No adjuvant treatment was administrated after resection. The mean duration of postoperative follow-up was 132 months (range, 97-198 months). There was no relapse in eight cases. Eight patients experienced tumor recurrence, with an average time to relapse of 70.3 months (range, 32-105 months), but without malignant transformation. Five of them have been re-treated, with a reoperation (two cases), chemotherapy (three cases) and radiotherapy (two cases). All patients continue to enjoy a normal life.

This is the first series demonstrating the prolonged impact of supratotal resection on malignant transformation of DLGG. These original data may suggest to remove a margin around the FLAIR-weighted MR imaging abnormalities in a more systematic manner for DLGG not involving eloquent structures [6].

2014

Nine consecutive patients were included in a study. There were 6 men and 3 women whose mean age was 35.5 years (range 22-59 years) at the time of initial symptom onset. All patients underwent surgery with the aid of intraoperative mapping, with incomplete tumor removal because of invasion of eloquent structures. The neuropathological examination diagnosed a DLGG in all cases (7 oligodendrogliomas, 1 astrocytoma, and 1 oligoastrocytoma). Five patients had a 1p19q codeletion. Because of tumor regrowth, the 9 patients underwent reoperation (2 surgeries in 6 cases and 3 surgeries in 3 cases), again with incomplete resection. There were no surgical complications. Adjuvant therapy (radiotherapy and chemotherapy) was administered in all patients because of progression to

a higher grade of malignancy that was histopathologically confirmed in all tumors. The patients suddenly worsened, and the diagnosis of LMSS was made with a mean delay of 77 months (range 27-140 months) after the initial symptom onset. Six patients benefited from salvage chemotherapy while palliative care was chosen in 3 cases. The median survival in the 6 patients who underwent LMSS treatment was significantly longer than that in the 3 patients who did not receive salvage chemotherapy ($p = 0.03$). Indeed, all patients died, with a mean delay between the diagnosis of LMSS and death of 11 months (range 2-38 months) and with a mean delay between the initial symptom onset and death of 88 months (range 34-144 months).

Cerebrospinal fluid dissemination of DLGG is a rare but possible event. It can occur throughout the progression of WHO Grade II oligodendrogliomas, oligoastrocytomas, and astrocytomas, regardless of 1p19q status. This complication seems to appear in patients who have undergone multiple incomplete resections. Salvage therapy can be considered in patients with good neurological status. However, LMSS is associated with a decreased overall survival. Therefore, this rare entity deserves further multicenter studies to better understand its pathophysiology and to adapt therapeutic strategies [7].

1)
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