The expression of the intercellular communication proteins GAP43 and Cx43 in diffuse and anaplastic gliomas.

Krigers A.1, Moser P.2, Fritsch H.3, Thomé C.1, Freyschlag C.F.1

1. Department of Neurosurgery, Medical University of Innsbruck
2. Department of Pathology, University Hospital Innsbruck
3. Section of Clinical and Functional Anatomy, Medical University of Innsbruck

Objectives. The expansion and therapeutic resistance of diffuse and anaplastic gliomas varies greatly. This might be possible due to variations in cell-to-cell communication, determined by the Cx43-associated junctional activity and microtubules-defined network, where the dominant structural component is GAP43. The aim of our trial was to assess the expression of these crucial proteins in samples of patients harboring WHO°II and III gliomas.

Methods. Tissue of adult patients with histologically proven WHO°II and III gliomas, who underwent surgery between 2014 and 2018, were selected from our institutional biobank. The GAP43 and Cx43 expression was analyzed using immunohistochemistry. The clinical and routine neuropathological findings were gained from patient charts.

Results. 43 (57%) males and 33 (43%) females with a median age of 47 (IQ: 35–61) years were analyzed. In 15 (20%) patients a diffuse low-grade glioma (WHO°II) and in 46 (60%) an anaplastic glioma (WHO°III) was diagnosed. Further 15 patients (20%) were diagnosed with a diffuse glioma showing only the focal anaplasia.

The IDH1 wildtype tumors showed a significantly higher expression of Cx43 (p=0.003) and a trend towards higher expression of GAP43 (p=0.075). Moreover, the IDH1 wildtype tumors demonstrated significantly higher Cx43 expression in patients with longer intervals between imaging-based diagnosis and actual biopsy (p=0.032), whereas this association was absent in IDH1 mutated gliomas (p=0.549). In the same time, advanced Cx43 expression correlated with lower Ki67 nuclear expression in both IDH1 wildtype (p=0.003) and mutated gliomas (p=0.019). In IDH1 wildtype gliomas the presence of ATRX was significantly associated with high GAP43 expression (p=0.031).

The GAP43 and Cx43 expression did not match the WHO grade; neither the age, gender or contrast enhancement in MR-imaging. There was no correlation with expression of EGFR, p53 or presence of 1p/19q co-deletion, MGMT-methylation and TERT status.

Discussion.
• The IDH1 wildtype gliomas showed advanced expression of Cx43 and GAP43 as well as longitudinal increase of Cx43.
• In the same time, tumors with lower mitosis rate produced more communication proteins, probably due to longer interphase. It can be interpreted as the intercellular networking provides acquired pathogenicity in the tumors with lower, e.g. “favorable”, proliferation rate.
• Moreover, IDH1 wildtype gliomas showed here advanced results, matching their aggressive behavior and poor outcome.
• Thus, diffuse and anaplastic gliomas are not homogenic and need to be evaluated considering their genetic profile.