Historical origin and meaning of the term „glial tumor“

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Abstract:

In everyday neurosurgical practice, the term „glial tumor“ is associated with astrocytomas, glioblastomas, and oligodendrogliomas, although historically this has not always been the case. The term „glial tumor“ was first given by Virchow in the 19th century as a term initially combining all primary brain tumors under this name. It derives from the name of the group of „supporting“ nerve cells - glia or neuroglia (from the Greek glia - glue), a group which for many years was wrongly ascribed only a cohesive or supporting function.

In 1926, in their classification of glial tumors - A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, one of the founding fathers of neuropathology Percival Bailey and the founding father of modern neurosurgery – Harvey Cushing ascribed several different tumors in this group: in addition to neuroepithelioma, spongioblastoma multiforme, astrocytoma and ependymoma, they also add medulloblastoma, astroblastoma, oligodendroglioma and unipolar spongioblastoma. Since then, the classification of glial tumors has undergone many changes to its current form. In the latest classification of brain tumors published in 2021, glial tumors are united in a common group together with glioneuronal and neuronal tumors. Their extensive group includes tumors with different prognosis, age presentation, molecular profile and therapeutic response. From a neurosurgical point of view, the term „glial tumor“ does not carry a prognostic value, but only determines the belonging of the tumor to the astrocyte, oligodendrocyte cell line or their precursor cells. In relation to that an interesting question arises- why the remaining tumors originating from glial cells other than astrocytic, such as ependymomas, lost their belonging to the group of glial tumors, or such as intracranial schwannomas, are not included in it at all.

Introduction

Over the years, from the beginning of the neuropathology as well as the oncological neurosurgical practice to the present day, the classification of glial tumors has undergone a number of changes, and the term „glial tumor“ has been used to refer to many different brain tumors. Originally, all brain tumors were called glial. Gradually, with the study of histogenesis and the introduction of modern methods of brain tumor research, this group changed its composition until the formation of its current view formulated in the latest revision of the classification of brain tumors of the World Health Organization (WHO) from 2021.

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Review

Glial tumors are the most extensive group of brain tumors. Known as early as 1800's when they were studied only grossly. At the time they were called by different modern terms: in England - „medullary sarcoma", in France known under the name „encephaloid", and in Germany „fungus medullare".[1] The name „glioma" was used for the first time by the German pathologist Virchow (1863/1865), who introduced the combined gross and histological approach to the study of brain tumors.[1]The origin of the word „glia" (from Greek „glue") dates back to the XIX century when it was mistakenly believed that glial cells or neuroglia served only to connect or glue together neurons. [2]Although the term „glia" has persisted through time until modern neuroscience, it is understood that glial cells have a number of other more essential functions besides the connective one. From anatomical point of view, astrocyte cells, ependymal cells, Oligodendrocytes and all originate from glial cells (neuroglia), which contradicts the modern concept of a glial tumor. In everyday neurosurgical practice, the term „glial tumor" is associated with astrocytomas, astroglial tumors including glioblastomas, and oligodendrogliomas, although historically this has not always been the case. [3–5] Throughout the years, the classification of glial tumors has undergone a number of changes to reach its current layout. The first report on the classification of brain tumors was published by Virchow in 1863. In his three-volume classification Die Krankhaften Geschwuelste 1862-1863, he divided brain tumors into two groups - sarcomas and gliomas, not on the basis of histogenesis, but on a descriptive sense. [1,5] The histological description he gave to what he named „gliomas" corresponds to and very well describeas the familiar astrocytomas, and as for Virchow's „sarcomas"- we now know as „glioblastomas".[1] Initially, sarcomas were described simply as tumors of mesenchymal origin without emphasizing their histological affiliation to glial tumors, due to the fact that the cells of these tumors were pathologically altered to such a degree that it was impossible to match the tissue from which they originated.[1]

The end of the 19th century and the beginning of the 20th century also marked the beginning of the histogenetic era in neuropathology, which lead to fundamental changes concerning the terms used. The glial origin of the tumors known as „sarcomas" now definitively proven lead to a change of term used to describe them to „gliosarcomas" and „glioma sarcomatodes". Gradually, in the following years, a number of important events took place in the history of neuropathology. Stroebe et al. in 1895 for the first time provided the first detailed microscopic descriptions of gliomas. Tooth et al. in 1912 for the first time included neurosurgical experience in the description of gliomas and reached important conclusions for their treatment.[6] Based on a ten-year study and a series of 500 patients, he concluded that glial tumors are in fact much more common than was known until then.[7] After the successful resection of two cerebral gliomas, without recurrence, he embraced the idea that glial tumors could be benign as well as malignant.[1, 7]

In 1926, Bailey and Cushing published their classification of glial tumors: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, on which the modern classification of glial tumors is based.[6, 7] Painfield et al. concluded that even before Bailey and Cushing published their work, the terms neuroepithelioma, spongioblastoma multiforme, or what is known today as glioblastoma, astrocytoma, and ependymoma were included in the group of „gliomas," but they added to this group four additional tumors: medulloblastoma, astroblastoma, oligodendroglioma, and unipolar spongioblastoma.[8] In 1949, Kernohan et al. simplified the classification by reducing the number of brain tumor types and introduced the concept of tumor grading.[9] Their work serves as a basis for formulating the modern classification and grading system for brain tumors of the World Health Organization (WHO).

The German neuropathologist Hans Joachim Scherer made huge contributions to the diagnosis and classification of glial tumors, although for many years he remained unappreciated for political reasons.[10] His work reached conclusions categorically proven and explained only after the introduction of molecular analysis and genetic research. For the first time, he introduced the term arising de novo „primary glioblastoma" and „secondary glioblastoma" – arising on the basis of a preceding low-grade neoplasia of the astrocytic line, paying attention not only to their origin, but also to the prognosis and differences in the course of the disease.[1] In the context of modern

terminology primary glioblastoma has a strong correlation with IDH-wildtype type glioblastoma and secondary glioblastoma strongly correlates with IDH-mutant type glioblastoma.

Despite the many available classifications of brain tumors until the middle of the 20th century, there was no unified classification accepted worldwide.

Currently, the accepted classification and grading system for brain tumors is that of the World Health Organization (WHO). The first edition of the WHO classification of brain tumors was published in 1979 based on the consensus of an international expert working group.[11] Since then, 5 editions of the classification of brain tumors have been published. The grouping of glial tumors changed accordingly as some of the tumors were taken off the group as others were added in. In the first edition of the classification of the WHO there was no separate group of glial tumors. Astrocytic tumors were in the group of tumors of neuroepithelial origin together with 7 other subgroups of tumors including: oligodendroglial, ependymal and choroid plexus tumors, pineal tumors, neuronal and a group of poorly differentiated and embryonal tumors.[14]The first WHO classification grouped glioblastomas separately from astrocytomas. They were grouped together with desmoplastic medulloblastoma and other tumors such as poorly differentiated tumors and embryonal tumors.[14] Astrocytomas were graded I, II and III, while Glioblastoma was considered grade IV. The stated facts underwent changes in the second edition of the classification of brain tumors of the WHO from 1993. Glioblastomas were included in the group of astrocytic tumors and a four-grade classification scale of astrocytomas was adopted.

In the 2007 edition of WHO classification of brain tumors, all astrocytic tumors were united in one general category. In the 2016 edition of the classification the glial tumors were separated into several groups: Diffuse astrocytic and oligodendroglial Tumours, Other astrocytic tumors, Other gliomas and Neuronal and mixed neuronal-glial tumors.[6] In the latest edition of the classification of brain tumors of the WHO from 2021 gliomas were united in one general group with glioneuronal tumors, and neuronal tumors. The new classification was created not only through modern molecular diagnostics, but through combination of established histological and immunohistochemical research methods as well. Based on this classification, only tumors belonging to the following four subgroups are considered glial tumors: Adult-type diffuse gliomas, Pediatric-type diffuse low-grade gliomas, Pediatric-type diffuse high-grade gliomas, Circumscribed astrocytic gliomas. Diffuse astrocytomas are divided into Adult-type diffuse gliomas and Pediatric-type diffuse low- and high-grade gliomas due to the clinical and molecular differences relative to the predominant age of the affected patients.[12]

Adult-type diffuse gliomas are the most common primary brain tumors in adults. They can rarely be observed in children. These include: Astrocytoma IDH-mutant grade 2, Astrocytoma IDH-mutant grade 3, Astrocytoma IDH-mutant grade 4, Oligodendroglioma grade 2 and grade 3, Glioblastoma IDH-wildtype. Although they are united mainly because of their age distribution in one group, the different tumors have a different prognosis: patients with IDH-mutant CNS WHO grade 2 astrocytomas have a median overall survival more than 10 years, and patients with grade 3 IDH-mutant astrocytomas have median overall survival in the range of 5–10 years, CNS WHO grade 4 astrocytomas with expected median overall survival of about 3 years.[13, 14]Pediatric-type diffuse low-grade gliomas have a relatively benign clinical course and relatively favorable prognosis than the tumors belonging to the group of Pediatric-type diffuse high-grade gliomas. The new classification largely combines clinical with morphological terminology: terms such as low-grade and high-grade tumors are no longer used, but circumscribed - correlates with grades 1 and 2 and diffuse gliomas - 3 and 4. Thus, there is a greater correlation between the neuroradiological appearance of the tumor, the type and extent of neurosurgical intervention and histopathology, since some groups may present primarily as diffuse, others only as circumscribed, as well as minor exceptions such as giant cell glioblastoma, which is neuroradiologically circumscribed.

Circumscribed astrocytic gliomas are distinguished by their limited non-diffuse growth pattern. From this group, pilocytic astrocytomas are an example of neoplasms that are associated with favorable overall survival rate for after complete resection they rarely recur.

In this context, it makes sense that future clinical terminology will be adapted to the modern histopathological knowledge- the term glioma carries little information with it, however circumscribed and diffuse, although non-specific are highly orienting for both the neurosurgeon, the pathologist, the oncologist and the radiation therapist.

Conclusion

Based on histogenesis the term glial tumor includes neoplasias based on astrocytic and oligodendrocytic cell lineages, and their precursors. Classifying a tumor as glial does not provide prognostic value and does not characterize the clinical course of the disease, nor its therapeutic response. However, due to its historical value, the term persists to this day and gives the name to the largest group of primary brain tumors.

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