Review of the World Health Organization classification of tumors of the nervous system

KEYWORDS: Nervous System Neoplasms; Classification; World Health Organization

Classification of tumors of the nervous system is a dynamic issue requiring permanent critical review because application of increasing number of new immunohistochemical and molecular genetic techniques give more precise data on the origin and nature of these tumors.

The first World Health Organization (WHO) classification of nervous system tumors (Zulch, 1979) had served its purpose very well during a period of almost ten years (1). The official revision of the 1979 WHO classification was done at the meetings in Houston (Texas, 1988) and in Zurich (Switzerland, 1990) and was published as the second WHO classification (2) 3 years later (Kleihues, 1993). Deliberations by the WHO experts committee at these two meetings were focused on three aspects: 1) the concept of primitive neuroectodermal tumor (PNET) and its relationship to medulloblastoma, 2) grading of glial tumors and 3) histo-biologic aspects of meningioma. A great innovation in the second WHO classification was introduction of immunohistochemistry as an additional factor in classification of tumors of nervous system. Several new tumor entities (pleomorphic xantoastrocytoma, central neurocytoma, infantile desmoplastic astrocytoma/ganglioglioma, dysembryoplastic neuroepithelial tumor) were included in these classifications.

The third WHO classification of the nervous system tumors was published in 2000 (3). This classification is based on consensus recommendation of an international WHO Working group of experts that convened in Lyon in 1999. The editors are P. Kleihues and W.K. Cavenee. The working methods comprised three steps: a consensus manuscript for each chapter was initially written by a limited number of selected authors; a revision of the manuscript by a wider subgroup of experts followed; and lastly, the final version was submitted to the entire working group. The 2000 WHO classification, in addition to histological and immunohistochemical basis (criteria) is supplemented by genetic results. During the past decade our knowledge of the genetic basis of human neoplasms has increased greatly and histological and immunohistochemical classification of neoplasms is now increasingly supplemented by genetic profiling. It is considered as a great step forward that for many neoplasms the cytogenetic and molecular genetic basis often represents a definitive criterion for classification. This trend will continue and the classification and possibly the grading of human neoplasms will increasingly be based on genomic alterations and gene expression patterns in addition to histopathological criteria. Histopathology and conventional light microscopy are still used in daily routine diagnosis as "gold standard" for diagnosis and classification of brain tumors, but it is nowadays evidently that immunohistochemistry, molecular genetics and electron microscopy are very important, sometimes indispensable adjunct for precise diagnosis within the existing classification, especially when dealing with poorly differentiated neoplasms.

The 2000 WHO classification is published in the form of the new Blue Book, which contains, in addition to definitions and codes of the International Classification of Diseases-Oncology (ICD-O), the comprehensive chapters describing the epidemiological, clinical, radiological, histopathological, biological and predictive features of each entity.

NEW TUMOR ENTITIES

The new tumor entities include chordoid glioma of the third ventricle, cerebellar liponeurocytoma, atypical teratoid/rhabdoid tumor, and paraneuroma (4).

Chordoid glioma of the third ventricle

This entity is added to the group neuroepithelial tumors of uncertain origin. It was first described as peculiar form of meningioma with expression of GFAP positivity. As chordoid glioma it was described in 1998 on the basis of eight cases restricted to the third ventricle. Histopathologically, this rare and slow growing tumor of adults corresponds to WHO grade II. It is composed of clusters of oval or polygonal cells with abundant eosinophilic cytoplasm, relatively uniform, often vesicular nuclei with small nucleoli and mucinous stroma. The mitoses are very rare or absent. A stromal lymphoplasmacytic infiltrate, often with Russell bodies is a consistent finding. Reactive astrocytes and Rosenthal fibers are seen in adjacent non neoplastic tissue. The tumor cells show strong diffuse reactivity for GFAP and vimentin, variable reactivity for S-100 protein, focally positive for epithelial membrane antigen (EMA), and negative for synaptophysin. There are histological similarities between chordoid glioma and chordoid meningioma, but chordoid meningioma is typically GFAP-negative, dura-based tumor (5).

Cerebellar liponeurocytoma

Cerebellar liponeurocytoma is a very rare, slowly growing neoplasm, with neuronal and lipomatous differentiation appearing exclusively in the cerebellum of adults. It was first reported in the 1978 under the name lipomatous medulloblastoma. Patients show typical clinical picture of a posterior fossa tumor. In cases reported to date there was no significant gender predilection. On the basis of the clinical, histological and immunohistochemical data, subsequently under different names (neurolipocytoma, lipomatous medulloblastoma, lipomatous glioneurocytoma, lipidized glioneuroectodermal tumor) this tumor was recognized as a separate clinicopathological entity and added to the category of neuronal and mixed neuronal-glial tumors in the 2000 WHO classification. Histopathologically, cerebellar liponeurocytoma is composed of small neoplastic cells that resemble neurocytes having round or oval nuclei and clear cytoplasm resembling neoplastic oligodendrocytes. Inside of these relatively uniform histological figure there are many smaller or larger groups of lipidized cells, resembling adipocytes. A hallmark of histological figure is presence of advanced neuronal differentiation. Necrosis and microvascular proliferation are absent pathological mitoses are rare. Immunohistochemically there is a diffuse positive expression of NSE, synaptophysin and MAP-2. GFAP is focally expressed in the majority of cases. The lipidized cells also show synaptophysin expression of the plasma membrane, indicating the lipidized neurocytic nature of these cells rather than being admixture of adipocytes. Cerebellar liponeurocytoma corresponds histologically to WHO grade I or WHO grade II (6).

Atypical teratoid/rhabdoid tumor (AT/RT)

AT/RT is a unique malignant embryonal CNS tumor occurring predominantly in infants and children. This tumor was first reported in 1985 and was originally designated as atypical teratoid tumor, but because of the histological...
similarities to the rhabdoid tumor of the kidney, the tumor designation was modified to AT/RT. In very rare cases AT/RT in infants was associated with primary renal rhabdoid tumor. About 200 cases have been reported until now, the great majority in children less than 5 years of age and only four cases in adults. There is a slight male preponderance. The tumor has tendency to be located in posterior fossa (cerebellum and cerebello-pontine angle), while supratentorial and spinal localization is less frequent. Cerebral and leptomeningeal dissemination is common, both at presentation and relapse. This tumor does not respond effectively to therapy and in great majority of cases it is fatal within one year. AT/RT corresponds histologically to WHO grade IV.

Grossly, AT/RT is similar to medulloblastoma or PNET. It is soft, pinkish, containing foci of necrosis and hemorrhage. In regions with mesenchymal tissue it tend to be firm and white-grayish. Microscopically, in addition to rhabdoid cells there are components of primitive neuroectodermal, mesenchymal and epithelial cells. Rarely the AT/RT is composed only of rhabdoid cells. The typical rhabdoid cells are round or oval, rich in cytoplasm, with typically eccentric nucleus and prominent nucleolus. Some cells contain poorly defined, pink inclusion body. Electronmicroscopically, rhabdoid cells are characterized by cyttoplasmic accumulation of intermediate filaments which push the nucleus to the cell periphery. Mesenchymal and epithelial components may exhibit high grade of malignancy. Mitotic activity is usually common in all cell components. Immunohistochemistry is very complex, depending upon the different tissue components. Rhabdoid cells express EMA and vimentin, and may express SMA, neurofilament, GFAP and keratin. Mesenchymal tissue expresses vimentin, sometimes SMA and desmin. Epithelial component expresses cytokeratin, sometimes EMA and vimentin (7).

Perineurioma
Perineurioma is a rare soft tissue benign tumour which is added to the group of peripheral nervous system tumours in the 2000 WHO classification. This tumor should be distinguished from the other nerve sheaths tumors. It can be divided broadly into two categories: intraneural perineurioma, localized intraneurally and more common soft tissue (extraneural) perineurioma, unassociated with nerve. Intraneural perineuriomas occur along the peripheral nerves of extremities in adults. Cranial nerves are extremely rare affected. Grossly, it is usually presented as solitary cylindrically enlargement of affected nerve up to 10 cm long. Soft tissue (extraneural), perineuriomas occur in superficial or deep soft tissue of adults with a female predilection (2:1). A malignant variant of perineurioma is extremely rarely reported. Microscopically, intraneural perineurimums are composed of perineurial cells encircling in more layers one or more axons forming pseudo-onion bulbs. Variable amount of collagenous stroma may be present between pseudo-onion bulbs and cell layers. Soft tissue perineuriums are composed of plump or spindled cells with one or more nuclei. These cells are arranged in whorls, bundles, interweaving fascicles, or they may show a storiform pattern. A variable amount of stromal fibrotic tissue surrounds these components.

Immunohistochemically, the tumour cells show EMA positive staining of the cellular component and collagen type IV positive staining of fibrotic stromal matrix. The tumour cells are negative for S-100 protein and cytokeratin. In intraneural perineurioma characteristic immunohistochemical feature is EMA-positive tumour cells and S-100 positive preexisting Schwann cells and neurofilament positive axons at the centers of the pseudo-onion bulbs. Monosomy of chromosome 22 has been demonstrated in both intraneural and soft tissue perineuriomas. Surgical treatment is curative and no recurrences or metastasis have been reported. Histologically, perineuriomas correspond to WHO grade I (8, 9).

REVISION OF THE MENINGIOMAS CATEGORY

Essential revision was introduced in the meningiomas category, regarding grade, histological subtype, proliferation index and brain invasion. For both atypical meningioma WHO grade II and anaplastic meningioma WHO grade III histopathological criteria are more precisely defined (10). Clear cell meningioma and chordoid meningioma are now assigned as WHO grade II because of relatively high recurrence rate after resection and rhabdoid meningioma as WHO grade III because of atypical histological features and aggressive course in most cases. It was recommended that brain invasion should be considered as stage of tumor development rather than malignancy grade.

RENAME TUMORS AND NOVEL TUMOR VARIANTS

Several tumors were renamed or established as novel tumor variants. The term mixed pineocytoma/pineoblastoma has been replaced by pineal parenchymal tumor of intermediate differentiation.

Tanyctic ependymoma (WHO grade II), large cell medulloblastoma (WHO grade IV), rhabdoid meningioma (WHO grade III) and teratoma with malignant transformation (no WHO grade) were established as novel tumor variants.

Peripheral neuroblastic tumors such as olfactory neuroblastoma (asthesioneuroblastoma, WHO III), olfactory neuroepithelioma (WHO grade III) and neuroblastoma of the adrenal gland and sympathetic nervous system (WHO grade III) are now included in the 2000 WHO classification as a separate chapter.

Polar spongioblastoma has been deleted from the current WHO classification since it is considered a growth pattern rather than a clinicopathological entity.

Several brain tumors, such as papillary gli-neuronal tumor, liposarcomatoma, lipomatous meningioma etc. that are recently reported in a few cases as possibly new clinicopathological entities or new variants, are not included in this classification because they have not been sufficiently studied.

CONCLUSION

Classifications of the nervous system tumors should be neither static nor definitive. The most recent, third, current WHO classification of nervous system tumors was published in 2000. Many substantial changes were introduced. New entities include the chordoid glioma of the third ventricle, the atypical teratoid/rhabdoid tumor, cerebellar liponeurocytoma (the former lipomatous medulloblastoma of the cerebellum), solitary fibrous tumor and perineurioma. The new tumor variants include the large cell medulloblastoma, tanyctic ependymoma and rhabdoid meningioma. Several essential changes were introduced in the meningiomas regarding histological subtypes, grading and proliferation index. In addition to new entities described in the 2000 WHO classification there are newly brain tumor entities and tumor variants, which are not included in the current classification due to the insufficient number of reported cases, for example papillary glioneuronal tumor, rosetted glioneuronal tumor, liposarcomatoma and lipomatous meningioma. They will be probably accepted in the next WHO classification. In the current WHO classification the importance of cytogenetic and molecular biologic investigation in the understanding and further classifications of these tumors has been emphasized.

REFERENCES

Epidemiology of central nervous system tumors

KEYWORDS: Nervous System Neoplasms; Classification; World Health Organization

Primary central nervous system (CNS) tumors are relatively infrequent in comparison with other malignant tumors. However, CNS tumors are the most frequent solid tumors in childhood and adolescence, accounting for approximately 20% of all malignant diseases in this age (1). There are many differences between childhood and adult CNS tumors according to frequency of some histologic types, biology, treatment, and prognosis.

Epidemiological analysis of the histologic features of CNS tumors in different ages showed that, in childhood, medulloblastoma ranks first among all tumors with participation of 24%, but it is not among the most common intracranial neoplasms in adults. Astrocytoma is second in children, whereas it is third in adults. Glioblastoma ranks third in children, but it makes up more than half of the CNS tumors in adults. Meningioma, which ranks second in adults, is relatively rare in children (2).

According to epidemiological literature, incidence of primary CNS tumors in a defined population varies from 4.9 to above 16/100 000 per year, while higher rates are generally found in societies with available and competent medical care, and with good organized cancer registries. Also, incidence rates are influenced by frequency of autopsy and improvement of case ascertainment with brain imaging technology such as CT and NMR (1,3). The American Cancer Society estimates that 16,800 new intracranial tumors were diagnosed in 1999, and the primary cancer of the CNS was the cause of death in 13 100 people in the same year (4). Some investigators report that the incidence of primary CNS tumors, especially in the elderly has substantially increased during the past two decades (3).

Despite variations among the different data sources in reporting and diagnostic practices, a general pattern of age-specific incidence was found: smaller peak in childhood can be seen, followed by a higher peak, reaching a maximum between 50 and 70 years of age, and then decline after those ages (2,4). Some authors stated that this decline is likely to be an artifact due to chance and bias. Elderly patients may be less likely to present themselves to a doctor due to symptoms of CNS tumor, may also be less likely to be referred for CT, or to have a necropsy if they are dead. The diagnostic bias may also be present in the very elderly people (5).

Mortality rates within each European area do not vary much, with the

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