Central Neurocytoma
Establishment of the Disease Entity

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KEYWORDS

• Central neurocytoma • Extraventricular neurocytoma • Atypical neurocytoma
• Neuronal differentiation • Disease entity

KEY POINTS

- Central neurocytoma was established as a distinct entity in the 1993 World Health Organization (WHO) classification.
- Extraventricular neurocytoma was established as a distinct entity in the 2007 WHO classification.
- Neuronal differentiation in gliomas is under active investigation, with new entities forthcoming.

INTRODUCTION

The existence of neuronal tumors in the central nervous system, aside from extreme cases of differentiation of neuronal lineages including gangliocytomas and neuroblastomas, was considered negligible until the 1980s.[1] However, sophisticated immunostaining and ultrastructural methods uncovered the "hidden face" of brain tumors undergoing neuronal differentiation. Central neurocytoma (CN) was a seminal discovery because it took a decade for the establishment of CN as a separate entity from its first report.[1,2] The original description of CN was specified as an exclusive, benign tumor undergoing neuronal differentiation located in the supratentorial ventricle.[3] However, evidence of diverse neurocytoma variants in the central nervous system has led to the establishment of a separate entity for extraventricular neurocytoma (EVN), which is beyond the classic concept of CN.[4] On the other hand, expanding knowledge of the neuronal component of brain tumors provides new insights for glial tumors undergoing neuronal differentiation, which has given rise to another source of controversy. The spectrum of neurocytomas, neuronal tumors with glial differentiation, glial tumors with neuronal differentiation, and gliomas should be considered comprehensively. However, evaluations of their clinical values are still premature. In this article, the steps of the establishment of this disease entity belonging to the neuronal tumor spectrum are retraced.

OLIGODENDROGLIOMA-LIKE NEURONAL TUMORS IN THE SUPRATENTORIAL VENTRICLE

CNs are rare, benign tumors composed of uniform, round cells undergoing neuronal differentiation, typically located in the intraventricular area around the foramen of Monro and the septum pellucidum.[5] Most affected patients are young adults or adolescents.[6] A diagnosis of CN is based on the neuronal characteristics of the tumor cells observed by immunohistochemistry and electron microscopy. Without testing for neuronal markers, CN has previously been misdiagnosed as intraventricular oligodendroglioma, ependymoma, or neuroblastoma, because of their morphologic similarities.[1,6] In 1982, Hassoun and colleagues[1] proposed the term "central neurocytoma" as a new entity based on its electron microscopic features. This tumor was so named because of its neuronal origin and midline location as well as to distinguish it from neuroblastoma, which is a more immature tumor type that mainly affects children.[3] In 1985,

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Wilson and colleagues[7] described CN as an oligodendroglioma-like tumor in the lateral ventricle, which they named "differentiated cerebral neuroblastoma" based on neuron-specific enolase immunostaining and electron microscopic findings. Other descriptions included "primary cerebral neuroblastoma" or "intraventricular neuroblastoma."[8–12] Confusing diagnoses continued through the 1980s, because many CNs were mistakenly categorized in a large series of neuroblastomas and oligodendrogliomas.[3,13] However, after more than 125 cases were reported in the literature, the incorporation of CN into the World Health Organization (WHO) classification as a distinct entity in 1993 ended the controversy.[2] CN is now a well-established entity in the WHO classification. Currently, more than 500 cases have been reported, representing 0.1% to 0.5% of all primary brain tumors.[6,14]

A diagnosis of CN still depends on immunohistochemical and ultrastructural methods. A wide variety of neuronal markers have been tested to ensure a more precise diagnosis of CN. Among the diverse immunohistochemical markers, synaptophysin is the most reliable.[6,15] Others, such as neuron-specific enolase and neuronal nuclear antigen, are also good markers for neoplastic neuronal cells in CN.[16,17] However, the neuronal phenotype of CN may not always implicate the same cell of origin. As the disease classification system of the WHO is based on the cell of origin, it is crucial to verify the cellular origin of the tumor. Unfortunately, the cellular origin of CN is still under debate. Multiple hypotheses exist, implicating neural cells, mixed neural-astrocytic cells, and neural stem cells as the cellular origins of CN.[18] Further investigations are needed to understand the hierarchy of oncogenesis in CN.

CENTRAL NEUROCYTOMA WITH AGGRESSIVE BEHAVIOR

The initial descriptions of benign cases designated CN as WHO grade I lesions; however, this classification was upgraded to WHO grade II in 1993, as a high proliferation index or histologic atypia was observed and occasional recurrences were reported.[2] Even so, most CN patients have a favorable prognosis after complete surgical resection.[6] The accumulation of data with regard to CN revealed that clinical behavior is not always benign but can be more malignant than expected. Studies reporting an aggressive clinical course of frequent recurrence after surgical resection in CN suggested the need for a possible modification of the disease entity.[19,20] There exist subsets of CN that harbor increased mitosis, microvascular proliferation, and necrosis.[21–25] However, separate grading or nosographic definitions have not been accepted, as those atypical histologic features are not generally predictive of an unfavorable prognosis.[14,26,27] A deeper understanding of the molecular pathogenesis is expected to provide classification criteria for the atypical/aggressive variant of CN.[18]

NEUROCYTOMA OUTSIDE THE VENTRICLE

The original diagnosis of CN was limited to tumors in the supratentorial ventricular system to avoid diagnostic ambiguity.[3] However, tumors with a similar histology to CN located outside the ventricle have been consistently reported.[28–30] In 1997, the first established study of EVN was reported by Giangaspero and colleagues.[31] EVN shows cytologic features similar to CN with small, round cells and a clear cytoplasm with a halo.[32] However, EVN demonstrates a much wider morphologic spectrum compared with classic CN, such as more glial components, ganglionic differentiation, atypical features of vascular proliferation, necrosis, and increased mitosis.[33] In addition, diverse extraventricular locations besides the cerebral hemispheres have been reported, including the thalamus, amygdala, sellar area, pons, cerebellum, spinal cord, and retina, as well as locations outside the central nervous system.[34–41] There were confusing diagnoses of ganglioneurocytoma, indicating neurocytoma undergoing differentiation into ganglion cells, which questioned whether a specific tumor was a variant of CN/EVN or a distinct tumor entity.[42] The controversy was settled after the 2007 WHO classification in which EVN was incorporated as a new entity and ganglioneurocytoma was eliminated.[4] Currently, CN and EVN coexist as independent entities of grade II tumors under the category of neuronal and mixed-neuronal glial tumors.[4] As in CN, EVN also can exhibit unusual features, either clinically or histologically, but the evidence is still too premature for the establishment of a typical/aggressive variant of EVN as a distinct entity.[33,43]

GLIAL TUMORS UNDERGOING NEURONAL DIFFERENTIATION

Evidence of neuronal differentiation is a potential touchstone for the future classification of neuroepithelial tumors of the central nervous system. Neoplastic components of neuronal differentiation can be defined by Homer-Wright or neurocytic rosettes, ganglioid cells, positive neuronal markers by immunohistochemistry, and ultrastructural features by electron microscopy. A combination of