KEY CONCEPTS

Toxic and Acquired Metabolic Diseases

- Certain vitamin deficiency states result in neurologic disease as well as systemic disorders, with thiamine and vitamin B_{12} being the two most common.
- The metabolic demand of the CNS makes it highly susceptible to injury from hypoglycemia and loss of oxygen-carrying capacity of hemoglobin with carbon monoxide toxicity.
- Chronic alcohol exposure may result in injury to the cerebellum, particularly to the anterior vermis.
- Metabolic disarray may disrupt brain function, often without detectable morphologic changes.

Tumors

The annual incidence of tumors of the CNS ranges from 10 to 17 per 100,000 persons for intracranial tumors and 1 to 2 per 100,000 persons for intraspinal tumors; the majority of these are primary tumors, and only one fourth to one half are metastatic. Tumors of the CNS account for nearly 20% of all cancers of childhood. Seventy percent of childhood CNS tumors arise in the posterior fossa; a comparable number of tumors in adults arise within the cerebral hemispheres above the tentorium.

While pathologists have developed classification schemes that distinguish between benign and malignant lesions on histologic grounds, the clinical course of a patient with a brain tumor is strongly influenced by patterns of growth and location. Thus, some glial tumors with low grade histologic features (low mitotic rate, cellular uniformity, and slow growth) infiltrate large regions of the brain and lead to serious clinical deficits and poor prognosis. Because of this capacity to diffusely infiltrate the white and gray matter, a tumor may not be amenable to complete surgical resection without compromising neurologic function. Also, any CNS neoplasm, regardless of histologic grade or classification, may have lethal consequences if situated in a critical brain region; for example, a benign meningioma may cause cardiorespiratory arrest if situated in the posterior fossa in a position to compress vital centers in the medulla. Even the most highly malignant gliomas rarely metastasize outside the CNS. Tumors are able to spread through the CSF if they encroach upon the subarachnoid space, and thus may be associated with implantation along the brain and spinal cord at a distance from the original tumor site.

Classification of tumors is one of the arts of pathology, drawing on traditional recognition of histologic and biologic features, combined with newer molecular analyses. Treatment protocols and experimental trials of glial tumors are usually based on the World Health Organization (WHO) classification, which segregates tumors into one of four grades according to their biologic behavior, ranging from grade I to grade IV. Under the current classification scheme, lesions of different grade are always given distinct names. When tumors recur, they often show progression to a higher histologic grade and designation; this actually represents clonal evolution of the same tumor, rather than a new disease. There is great interest in identifying tumor-initiating (or stem-like) cells that maintain tumor growth and, therefore, may be key targets of new therapies.

The major classes of primary brain tumors to be considered here include gliomas, neuronal tumors, poorly differentiated tumors, and a group of other less common tumors. In addition, we will discuss tumors of the meninges as well as familial tumor syndromes.

Gliomas

Gliomas, the most common group of primary brain tumors, include *astrocytomas*, *oligodendrogliomas*, and *ependymomas*. These tumor types have characteristic histologic features that form the basis for the classification. It is no longer thought that these tumors derive from their specific, mature cell types (astrocytes, oligodendrocytes, and ependymal), but rather that they arise from a progenitor cell that preferentially differentiates down one of the cellular lineages. Many of the tumors typically occur in certain anatomic regions within the brain, with characteristic age distribution and clinical course.

Astrocytoma

The two major categories of astrocytic tumors are the diffusely infiltrating astrocytomas and the more localized astrocytomas, of which the most common are the pilocytic astrocytomas. Astrocytomas may range from WHO grade I to grade IV, may occur from the first decade of life onward and may be found anywhere along the neuroaxis from the cerebral hemispheres to the spinal cord.

Infiltrating Astrocytomas

Infiltrating astrocytomas account for about 80% of adult primary brain tumors in adults. Usually found in the cerebral hemispheres, they may also occur in the cerebellum, brainstem, or spinal cord, most often in the fourth through sixth decades. The most common presenting signs and symptoms are seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement. Infiltrating astrocytomas show a spectrum of histologic differentiation that correlates well with clinical course and outcome; within this spectrum, tumors range from *diffuse astrocytoma* (grade II/IV) to *anaplastic astrocytoma* (grade III/IV) to *glioblastoma* (grade IV/IV). There are no WHO grade I infiltrating astrocytomas.

Molecular Genetics. It was recognized well before modern advances in genetic analyses that glioblastoma tends to occur in one of two clinical settings—most commonly as a new onset disease, typically in older individuals *(primary glioblastoma)*, and less frequently in younger patients due to progression of a lower-grade astrocytoma *(secondary glioblastoma)*. Data from the Cancer Genome Atlas Network based on sequencing the genome of malignant gliomas have identified **patterns of molecular alteration in glioblastoma that place these tumors into four molecular subtypes: classic, proneural, neural, and mesenchymal**.

- The *classic subtype*, comprising the majority of primary glioblastoma, is characterized by mutations of the *PTEN* tumor suppressor gene, deletions of chromosome 10, and amplification of the *EGFR* oncogene. Focal deletions