the risk for hemorrhage into the tumor. Inferior vena cava filters are reserved for patients with absolute contraindications to anticoagulation such as recent craniotomy.

PRIMARY BRAIN TUMORS

PATHOGENESIS

No underlying cause has been identified for the majority of primary brain tumors. The only established risk factors are exposure to ionizing radiation (meningiomas, gliomas, and schwannomas) and immunosuppression (primary CNS lymphoma). Evidence for an association with exposure to electromagnetic fields including cellular telephones, head injury, foods containing *N*-nitroso compounds, or occupational risk factors are unproven. A small minority of patients have a family history of brain tumors. Some of these familial cases are associated with genetic syndromes (Table 118-2).

As with other neoplasms, brain tumors arise as a result of a multistep process driven by the sequential acquisition of genetic alterations. These include loss of tumor-suppressor genes (e.g., *p53* and phosphatase and tensin homolog on chromosome 10 [*PTEN*]) and amplification and overexpression of protooncogenes such as the epidermal growth factor receptor (*EGFR*) and the platelet-derived growth factor receptors (*PDGFR*). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation.

Important progress has been made in understanding the molecular pathogenesis of several types of brain tumors, including glioblastoma and medulloblastoma. Morphologically indistinguishable glioblastomas can be separated into four subtypes defined by molecular profiling: (1) classical, characterized by overactivation of the EGFR pathway; (2) proneural, characterized by overexpression of PDGFRA, mutations of the isocitrate dehydrogenase (*IDH*) 1 and 2 genes, and expression of neural markers; (3) mesenchymal, defined by expression of mesenchymal markers and loss of *NF1*; and (4) neural, characterized by overactivity of EGFR and expression of neural markers. The clinical implications of these subtypes are under study. Medulloblastoma is the other primary brain tumor that has been highly analyzed, and four molecular subtypes have also been identified: (1) the Wnt subtype is defined by a mutation in β-catenin and has an excellent prognosis; (2) the SHH subtype has mutations in *PTCH1*, *SMO*, *GLI2*, or *SUFU* and has an intermediate prognosis; (3) group 3 has elevated MYC expression and has the worst prognosis; and (4) group 4 is characterized by isochromosome 17q. Targeted therapeutics are under development for some of the medulloblastoma subtypes, especially the SHH group.

INTRINSIC "MALIGNANT" TUMORS

ASTROCYTOMAS

These are infiltrative tumors with a presumptive glial cell of origin. The World Health Organization (WHO) classifies astrocytomas into four prognostic grades based on histologic features: grade I (pilocytic astrocytoma, subependymal giant cell astrocytoma); grade II (diffuse astrocytoma); grade III (anaplastic astrocytoma); and grade IV (glioblastoma). Grades I and II are considered low-grade astrocytomas, and grades III and IV are considered high-grade astrocytomas.

Low-Grade Astrocytoma These tumors occur predominantly in children and young adults.

GRADE I ASTROCYTOMAS Pilocytic astrocytomas (WHO grade I) are the most common tumor of childhood. They occur typically in the cerebellum but may also be found elsewhere in the neuraxis, including the optic nerves and brainstem. Frequently they appear as cystic lesions

TABLE 118-2 GENETIC SYNDROMES ASSOCIATED WITH PRIMARY BRAIN TUMORS

Syndrome	Inheritance	Gene/Protein	Associated Tumors
Cowden's syndrome	AD	Mutations of *PTEN* (ch10p23)	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), meningioma, astrocytoma
			Breast, endometrial, thyroid cancer, trichilemmomas
Familial schwannomatosis	Sporadic Hereditary	Mutations in *INI1/SNF5* (ch22q11)	Schwannomas, gliomas
Gardner's syndrome	AD	Mutations in *APC* (ch5q21)	Medulloblastoma, glioblastoma, craniopharyngioma
			Familial polyposis, multiple osteomas, skin and soft tissue tumors
Gorlin syndrome (basal cell nevus syndrome)	AD	Mutations in *Patched 1* gene (ch9q22.3)	Medulloblastomas
			Basal cell carcinoma
Li-Fraumeni syndrome	AD	Mutations in *p53* (ch17p13.1)	Gliomas, medulloblastomas
			Sarcomas, breast cancer, leukemias, others
Multiple endocrine neoplasia 1 (Werner's syndrome)	AD	Mutations in *Menin* (ch11q13)	Pituitary adenoma, malignant schwannomas
			Parathyroid and pancreatic islet cell tumors
Neurofibromatosis type 1 (NF1)	AD	Mutations in *NF1*/neurofibromin (ch17q12-22)	Schwannomas, astrocytomas, optic nerve gliomas, meningiomas
			Neurofibromas, neurofibrosarcomas, others
Neurofibromatosis type 2 (NF2)	AD	Mutations in *NF2*/merlin (ch22q12)	Bilateral vestibular schwannomas, astrocytomas, multiple meningiomas, ependymomas
Tuberous sclerosis (TSC) (Bourneville disease)	AD	Mutations in *TSC1/TSC2* (ch9q34/16)	Subependymal giant-cell astrocytoma, ependymomas, glioma, ganglioneuroma, hamartoma
Turcot syndrome	AD	Mutations in *APC*[a] (ch5)	Gliomas, medulloblastomas
	AR	hMLH1 (ch3p21)	Adenomatous colon polyps, adenocarcinoma
von Hippel–Lindau (VHL)	AD	Mutations in *VHL* gene (ch3p25)	Hemangioblastomas
			Retinal angiomas, renal cell carcinoma, pheochromocytoma, pancreatic tumors and cysts, endolymphatic sac tumors of the middle ear

[a]Various DNA mismatch repair gene mutations may cause a similar clinical phenotype, also referred to as Turcot syndrome, in which there is a predisposition to nonpolyposis colon cancer and brain tumors.

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; ch, chromosome; PTEN, phosphatase and tensin homologue; TSC, tuberous sclerosis complex.