

Nervous system: Astrocytic tumors

Classification

Note Astrocytic tumors comprise a wide range of neoplasms that differ in their location within the central nervous system (CNS), age and gender distribution, growth potential, extent of invasiveness, morphological features, tendency for progression and clinical course; there is increasing evidence that these differences reflect the type and sequence of genetic alterations acquired during the process of transformation. The following clinicopathological entities can be distinguished :

- Pilocytic Astrocytomas (Grade I)
- Fibrillary Astrocytomas (Grade II)
- Anaplastic Astrocytomas (Grade III)
- Glioblastoma Multiforme (Grade IV)

Clinics and Pathology

Etiology gliomas have been observed following therapeutic irradiation. familial clustering of gliomas is not uncommon: the association with defined inherited tumor syndrome including the [Li-Fraumeni syndrome](#), [Turcot syndrome](#), and the [NF1 syndrome](#)

Epidemiology diffuse astrocytomas are the most frequent intracranial neoplasm and account for more than 60% of all primary brain tumors; the incidence differs between regions, but there are 5 to 7 new cases per 100.000 population per year

Clinics

1. Pilocytic Astrocytomas / Grade I: pilocytic astrocytomas arise throughout the neuraxis and are common in children and in young adults; pilocytic tumors of the optic nerve cause loss of vision; pilocytic astrocytoma of the hypothalamus and third ventricular region primarily affect children; but tumors of the cerebral hemispheres generally occur in patients older than those with visual system or hypothalamic involvement
2. Fibrillary Astrocytomas / Grade II: fibrillary astrocytomas arise in the cerebral hemisphere of young to middle-aged adults and the brain stem of children; occasional examples occur in the cerebellum or spinal cord; at any site these astrocytomas must be distinguished from pilocytic astrocytomas; all such tumors are pilocytic astrocytomas in the optic nerve whereas most are of the fibrillary type in the brain stem
3. Anaplastic Astrocytomas / Grade III: anaplastic astrocytomas occur in the same locations as astrocytomas (I-II) and glioblastoma, but the majority affect the cerebral hemispheres; anaplastic astrocytomas generally occur in patients a decade older than those with better differentiated astrocytomas and a decade younger than those with glioblastomas

4. Glioblastoma Multiforme / Grade IV: glioblastoma is by far the most common glioma; it affects principally the cerebral hemispheres in adults and the brain stem in children; but they are most frequent after the fifth decade; most glioblastomas are solitary but occasional examples are geographically separate in the same patient and warrant the designation " multicentric "; usually, it appears as a central area of hypodensity surrounded by a ring of contrast enhanced and penumbra of cerebral oedema
glioblastoma multiforme may develop de novo (primary glioblastoma) or through progression from low-grade or anaplastic astrocytoma (secondary glioblastoma); patients with a primary glioblastoma are usually older, present a rapid tumor progression and a poor prognosis; patients with secondary glioblastomas are younger and tumors progress more slowly, with a better prognosis; these two groups are histologically indistinguishable

Pathology

1. Pilocytic Astrocytomas / Grade I: this predominantly pediatric brain tumor is a circumscribed astrocytoma composed in varying proportions of compacted and loose textured astrocytes associated with Rosenthal fibers, eosinophilic granular bodies, or both; the lesion described is sometimes referred to as the " juvenile pilocytic astrocytoma "
2. Fibrillary Astrocytomas / Grade II: this tumor is a well differentiated diffusely infiltrating neoplasm of fibrillary astrocytes
3. Anaplastic Astrocytomas / Grade III: this tumor is an astrocytic tumor of fibrillary type which is intermediate in differentiation between the better differentiated astrocytoma and glioblastoma; it is an astrocytic neoplasm that typically exceeds well differentiated astrocytoma in terms of cellularity, nuclear pleomorphism and hyperchromasia necrosis of glioblastoma
4. Glioblastoma Multiforme / Grade IV: this tumor is a highly malignant glioma most closely related to fibrillary or diffuse astrocytic neoplasms; glioblastomas are cellular masses with varied tissue patterns; it appears either infiltrating or discrete, with typical or atypical mitoses, endothelial vascular proliferation and necrosis

another subgroup of glioblastoma can be distinguished: the giant cell glioblastomas; histologically it is a glioblastoma with giant cells (500 μm in diameter): it develops clinically "de novo "; it is associated with a favorable prognosis

Treatment

treatment differs according to grade and location of tumor
pilocytic astrocytomas can be cured by complete resection of tumor; if exeresis is not possible due to the location of the tumor, chemotherapy is indicated in young children and radiotherapy in adults
in fibrillary astrocytomas, the treatment consists of total and extent resection of tumor

Prognosis in anaplastic tumors and glioblastoma multiforme, the treatment consists of total resection and radiotherapy and chemotherapy after surgery in low grade astrocytomas, a correlation of proliferation was reported (Ki67 index) with clinical outcome; the proliferative potential correlates inversely with survival and time to recurrence; the mean survival time after surgery is 6-8 years in low-grade astrocytomas; after surgery, the prognosis depends on whether the neoplasm undergoes progression to a more malignant phenotype; in pilocytic astrocytomas, total cure is possible after total resection; in fibrillary astrocytomas recurrence is frequent

. in anaplastic astrocytomas and in glioblastomas, evaluation of the extent of resection can be a prognostic factor; prognosis is generally poor (about one year); patients below 45 yrs have a considerably better prognosis than elderly patients; primary glioblastomas have a short clinical history with a poor prognosis; survival is better in secondary glioblastomas

Cytogenetics

Cytogenetics In astrocytomas grade I, normal karyotype is observed most frequently; among the cases with abnormal karyotypes, the most frequent chromosomal abnormality is loss of the X and Y sex-chromosomes; loss of 22q is found in 20-30% of astrocytomas; other abnormalities observed in low grade tumors include gains on chromosome 8q, 10p, and 12p, and losses on chromosomes 1p, 4q, 9p, 11p 16p, 18 and 19

In anaplastic astrocytomas, chromosome gains or losses are frequent: trisomy 7 (the most frequent), loss of chromosome 10, loss of chromosome 22, loss of 9p, 13q; other abnormalities, less frequently described are: gains of chromosomes 1q, 11q, 19, 20, and Xq

Glioblastomas show several chromosomal changes: by frequency order, gain of chromosome 7 (50-80% of glioblastomas), double minute chromosomes, total or partial monosomy for chromosome 10 (70% of tumors) associated with the later step in the progression of glioblastomas partial deletion of 9p is frequent (64% of tumors): 9pter-23; partial loss of 22q in 22q13 is frequently reported loss or deletion of chromosome 13, 13q14-q31 is found in some glioblastomas

trisomy 19 was reported in glioblastomas by cytogenetic and comparative genomic hybridization (CGH) analysis; the loss of 19q in 19q13.2-qter was detected by loss of heterozygosity (LOH) studies in glioblastomas

deletion of chromosome 4q, complete or partial gains of chromosome 20 has been described; gain or amplification of 12q14-q21 has been reported

the loss of chromosome Y might be considered, when it occurs in addition to other clonal abnormalities

Genes involved and Proteins

Note Alteration of genes involved in cell-cycle control: it is known that the progression of the-cell cycle is controlled by positive and negative regulators; some authors report alteration in cell-cycle gene

expression in human brain tumors

the [p16](#) gene and the p15 gene are located in 9p21, a chromosome region commonly deleted in astrocytomas; expression of p16 gene is frequently altered in these tumors: in 33-68% of primary glioblastomas and 25% of anaplastic astrocytomas

the [Rb](#) gene located on 13q chromosome plays an important role in the malignant progression of gliomas

the [p53](#) gene is a tumor suppressor gene located on chromosome 17p13.1; loss or mutation of p53 gene has been detected in many types of gliomas and represents an early genetic event in these tumors overexpression of MDM2 is also seen in primary glioblastomas others oncogenes have been found to be amplified in a few cases of astrocytomas : oncogenes [Gli](#), [MYC](#), [MYCN](#), [MET](#) and [N-Ras](#)

Loss or inactivation of tumor suppressor genes:

in addition to p53 gene, others tumor suppression genes play a role in astrocytomas

loss of chromosome 10 is the most frequent abnormality associated with the progression of malignant astrocytic tumors; more than 70% of glioblastomas show LOH on chromosome 10; amplification of EGFR is always associated with loss of chromosome 10

the [PTEN](#) gene located at the 10q23 locus is implicated more frequently in glioblastomas than in anaplastic astrocytomas

another suppressor gene the [MXI1](#) gene has also been located on the distal portion of chromosome 10 at the 10q24 at the 10q24-p25 locus homozygous deletion in the DMTB gene located on the region 10q25.3-26.1 have been reported in glioblastomas

the LG11 novel gene located in 10p24 region is a suppressor gene rearranged in several glioblastomas tumors

allelic loss of chromosome 22q which contains the neurofibromatosis type 2, tumor suppressor gene [NF2](#) is observed in 20-30% of astrocytomas.

But another possibility is the involvement of another gene located on chromosome 22 in the tumorigenesis of astrocytomas

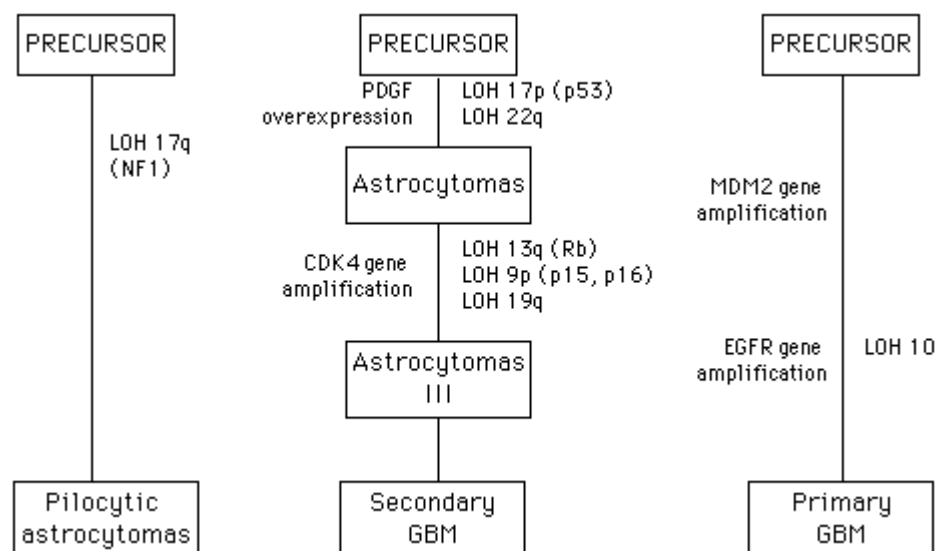
most of these genes participate in the progression of astrocytomas (fig 1)

Expression of growth factors and growth factor receptors:

the epidermal growth factor receptor (EGFR) coded by the EGFR cellular oncogene is located on human chromosome 7 at locus 7p12-p14; EGFR is amplified in 40-60% of glioblastomas; it constitutes a hallmark: primary glioblastomas rarely contain EGFR overexpression; patients with anaplastic astrocytomas or glioblastomas have a poorer prognosis when EGFR gene amplification is present; amplification could be a significant prognostic factor in these tumors

over expression of PDGFR- α (platelet derived growth factor) is associated with loss of heterozygosity of chromosome 17p and p53 mutations in secondary glioblastomas

others growth factors expressed in gliomas include fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), and vascular endothelial growth factor (VEGF)



Molecular pathways in the progression of astrocytomas (from Ho-Keung and Paula Y.P. Lam)

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Contributor(s)

Written 11-2000 Anne Marie Capodano

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