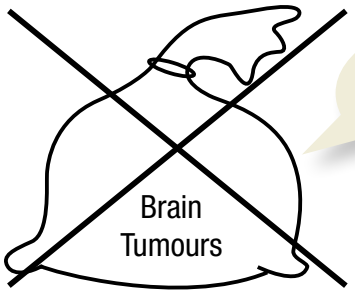
1 Epidemiology, pathogenesis and risk factors of brain tumours

Introduction; definition

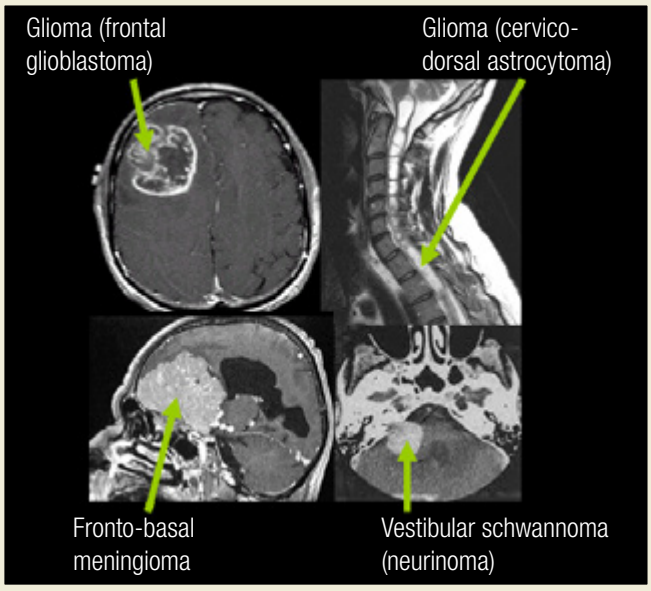
"Brain tumours" is the common term to define central nervous system (CNS) neoplasms, or CNS tumours.

The global incidence of all CNS tumours is unknown but higher than 45/100 000 patients a year.

The 2016 World Health Organization classification of CNS tumours is based on histopathological and molecular criteria and includes malignant, benign and borderline tumours. They are categorised as primary or secondary.



Brain tumours are not one entity, but diverse histological entities with different causes, prognosis and treatments.



Primary CNS tumours include all primary tumours located in the CNS, the envelopes of the CNS and the beginning of the nerves localised in the skull and spine.

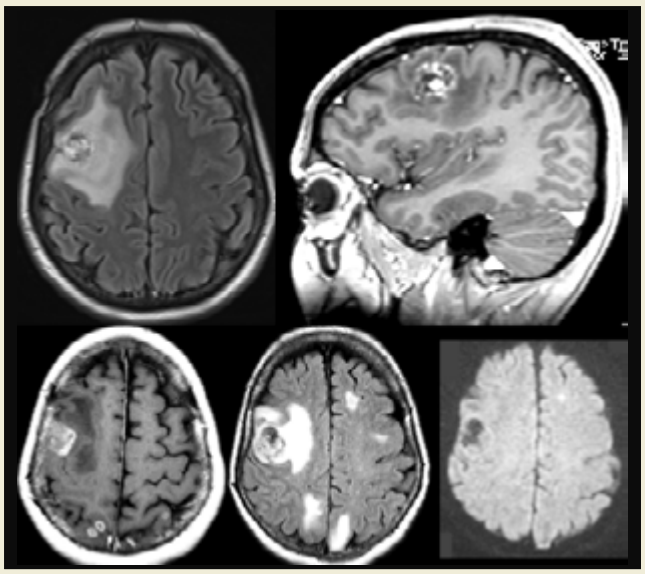
In the USA, the incidence rate of all primary malignant and non-malignant CNS tumours is 21.42/100 000 (7.25/100 000 for malignant and 14.17/100 000 for non-malignant tumours).

In the USA, among the various histological groups of primary CNS tumours, meningiomas account for 36%, gliomas for 28%, nerve sheath tumours for 8% and lymphomas for 2%.

Secondary CNS tumours are CNS metastases; they are all malignant. CNS metastases are single or multiple.

Metastatic tumours are the most frequent type of CNS tumour in adults. The reported incidence of metastatic CNS tumours is increasing but the exact incidence is unknown.

In general, the sources of brain metastases (in descending order) are: cancers of the lung, breast, skin (melanoma), kidney and gastrointestinal tract.



REVISION QUESTIONS

1. Do brain tumours always have the same origin?
2. Name the two most common histological groups among primary tumours.
3. Which brain tumours are more frequent: primary or secondary?

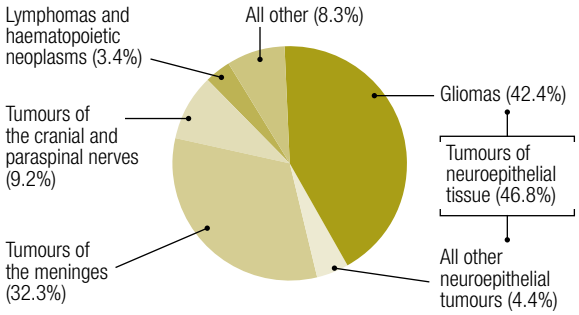
Primary CNS tumours – descriptive epidemiology

Epidemiological data on primary CNS tumours come from registries and population studies. But registration guidelines and population vary among registries and countries, so results from the literature should be analysed according to these differences.

Primary CNS tumours are divided into major histological groups.

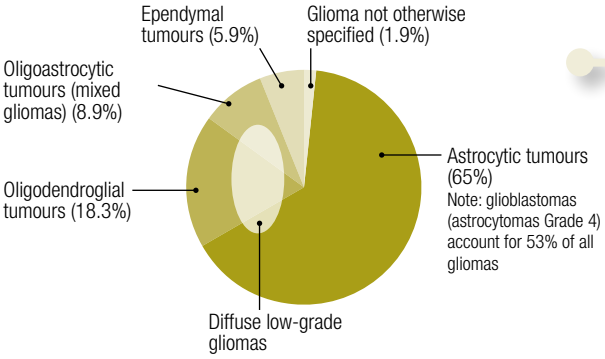
More than 90% of neuroepithelial tissue tumours are malignant, and more than 90% of meningeal tumours are non-malignant.

Distribution of all primary CNS tumours by major histology groupings in France



CNS, Central nervous system.

Distribution of gliomas by major histological subgroups in France



In adults, the male/female ratio for diffuse gliomas is approximately 1.5. Among these, glioblastoma (Grade 4 glioma) is the most frequent. The median age at diagnosis is 64 years.

Diffuse Grade 2 gliomas (DGIIGs, often named diffuse low-grade gliomas) and diffuse Grade 3 gliomas (DGIIIGs, often named anaplastic gliomas) account for approximately 30% of all gliomas.

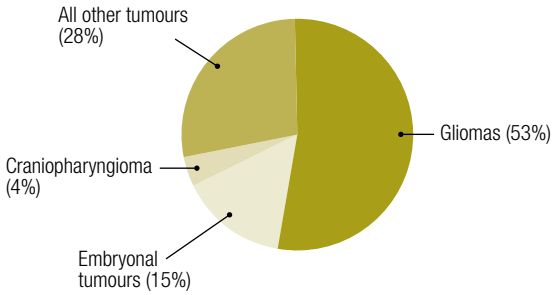
Median age at diagnosis is 43 years for DGIIG and 56 years for DGIIIG.

In the USA, the incidence rate of paediatric (<15 years old) primary CNS tumours is 5.3 cases per 100 000. These tumours are the most common paediatric solid tumours.

Paediatric gliomas include pilocytic astrocytomas (Grade 1 glioma, 33%), Grade 3 and 4 gliomas (21%), ependymal tumours (10%) and all other gliomas (36%).

All embryonal tumours are malignant. Medulloblastoma is the most important subgroup of embryonal tumours (62%).

Distribution of all paediatric primary CNS tumours by major histology groupings (0-14 years) in USA



CNS, Central nervous system.

REVISION QUESTIONS

1. Why can epidemiological data differ from one country to the next?
2. Are diffuse gliomas more frequent in women or men?
3. What is the most frequent grade of glioma in children?

Primary CNS tumours – clinical epidemiology

Prognostic factors and therapeutic measures (resection, radiotherapy, chemotherapy, new therapy) impact survival in primary CNS tumour patients.

Multivariate analysis is one method used to take into account different prognostic factors for the survival analysis.

Usually, median survival in population studies (all patients [with good or poor prognostic factors] are included) is shorter than in clinical trials (only selected patients are included).

Main prognostic factors for primary CNS tumours

Age
Performance status (e.g. Karnofsky performance status)
Comorbidity
Appearance of the tumour by MRI (topography, volume, delimitation, enhancement, etc.)
Features of the new tumour imaging techniques (multimodal MRI, PET scan, etc.)
Tumour growth rate
Histological type and subtype
Histological grade
Biology
Etc.

CNS, Central nervous system; MRI, magnetic resonance imaging; PET, positron emission tomography.

Survival rate (SR) for selected gliomas and age groups (years) in USA

Histology	Age group	1-Year SR (%)	10-Year SR (%)
Pilocytic astrocytoma	0-14	98.8	95.9
	15-39	97.2	90.2
	40+	95.3	72.4
Oligodendroglioma	0-14	96	90.9
	15-39	98.6	69.7
	40+	90.3	54.6
Glioblastoma	0-14	49.9	14.9
	15-39	71.7	13.2
	40+	34.2	1.6

See CBTRUS table for 95% confidence intervals: http://www.cbtrus.org/reports/reports.html

Glioblastoma is the most frequent glioma with the worst prognosis (median survival ≈10 months in population studies, and 14.6 months in the group of patients treated with radiotherapy and temozolomide in the pivotal study of Stupp et al).

Most children with pilocytic astrocytoma who have a complete resection are cured without further oncological treatment.

The quality of life (QoL) of oligodendroglioma patients is often preserved for several years with surgery(ies) and oral chemotherapy.

The QoL of primary CNS tumour patients is often affected by a variety of symptoms, depression and fatigue. Diagnosis of a brain tumour is a life-changing event for patients and families.

Helping these patients, treating symptoms and improving QoL at all stages of illness are important goals for the multidisciplinary care team.

Supportive care teams can improve the patient's QoL, symptom burden and even survival.

Signs and symptoms (%) in a series of 7786 primary CNS tumour patients

	Ep	Ha	RI	MD	FD	Ot	As
Gliomas	31	29	22	30	41	7	3
Other NET	26	38	49	11	17	11	3
Meningiomas	24	33	14	20	34	18	7
Lymphomas	14	27	19	53	48	7	1

As, Asymptomatic; CNS, central nervous system; Ep, epilepsy; FD, focal deficit; Ha, headache; MD, mental status disorders; NET, neuroepithelial tumours; Ot, other; RI, raised intracranial pressure.

REVISION QUESTIONS

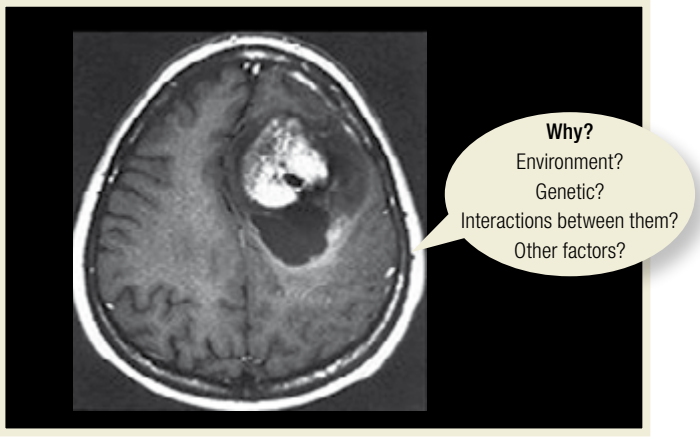
1. Age at diagnosis is the only prognostic factor in gliomas. True or false?
2. What is the median survival for glioblastoma patients in population studies?
3. What are the main clinical symptoms in primary CNS tumour patients?

Gliomas and meningiomas – risk factors

High-dose ionising radiation is the only unequivocal environmental risk factor that was identified for glial and meningeal neoplasms. An association was observed in A-bomb studies, nuclear test fallout data, therapeutic radiation, and occupational and environmental studies.

In 2011, the International Agency for Research on Cancer classified mobile phone use and other radiofrequency electromagnetic fields as a possible carcinogenic agent (Group 2B).

Many environmental risk factors (non-ionising radiation, e.g. mobile phones, pesticides, solvents, etc.) have been examined as potential contributors to glioma risk, with inconclusive results until now.



Monogenic Mendelian disorders associated with increased risk of glioma

Gene	Disorder/syndrome
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
TSC1,TSC2	Tuberous sclerosis
MSH2, MLH1, MSH6, PMS2	Lynch syndrome
TP53	Li-Fraumeni syndrome
p16/CDKN2A	Melanoma-neural system tumour syndrome
IDH1/IDH2	Ollier disease/Maffucci syndrome

A heritable genetic contribution to glioma genesis was initially suggested by the increased incidence of these tumours in families with Mendelian cancer syndromes.

But a very small portion of these tumours are caused by Mendelian disorders, including neurofibromatosis, tuberous sclerosis and Li-Fraumeni syndrome.

Excluding genetic syndromes, familial cases of primary CNS tumours represent less than 5% of cases.

Epidemiological studies consistently suggest that allergic conditions, including asthma, hay fever, eczema and food allergies, are associated with reduced glioma risk.

In the USA, incidences of glioblastoma and oligodendroglioma are approximately 2 times greater in white people than in black people, but the incidence of meningioma is higher in black people than white people.

Genome-wide association studies have identified heritable risk alleles within 7 genes that are associated with increased risk of glioma.

Candidate genes	Chromosome location
TERT	5p15.33
EGFR	7pl1.2
CCDC26	8q24.21
CDKN2B	9p21.3
PHLDBI	11q23.3
TP53	17pl3.1
RTELI	20ql3.33

REVISION QUESTIONS

1. What is the only identified environmental risk factor that increases the risk of glioma or meningioma?
2. What are the rare genetic syndromes associated with gliomas?
3. Allergy is associated with a reduced risk of glioma. True or false?

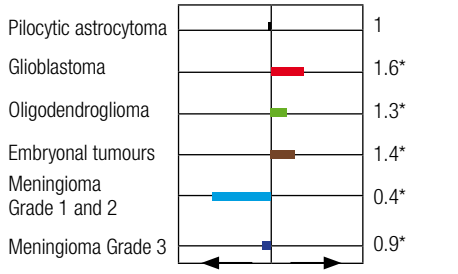
Gliomas and meningiomas – risk factors (continued)

Across countries and populations, the incidence of brain tumours is related to gender, with opposite patterns for meningiomas and gliomas. The male/female ratio for meningioma is approximately 0.4 (1 man for 2.5 women).

This difference suggests that sex hormones and/or genetic differences between males and females may play a role in the occurrence of these tumours.

Hormonal receptors were identified in meningioma tissues: ≈80% of meningiomas have progesterone receptors, 40% oestrogen receptors and 40% androgen receptors.

Incidence rate ratios by gender (males/females) in USA



Higher incidence in females I Higher incidence in males
*Significant difference

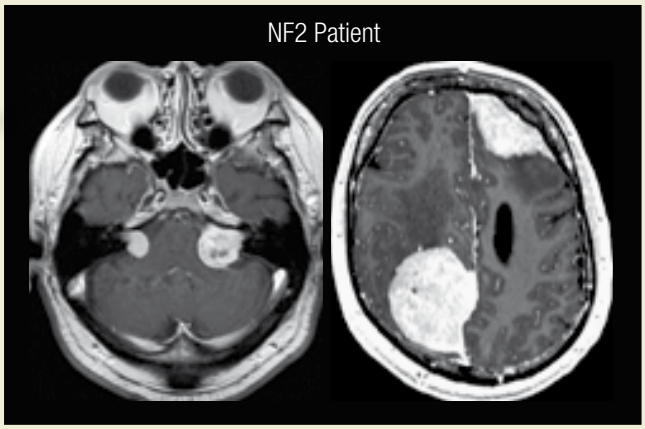
Menopausal hormone therapy is associated with an increased meningioma risk. A recent meta-analysis suggests an increased risk in users of oestrogen-only hormone therapy.

Oral contraception and breast-feeding do not appear to increase the risk of meningioma.

To date, among exogenous suspected factors (electromagnetic fields, nutrition, pesticides, etc.), the only established causal link with risk of meningioma is high doses of ionising radiation.

Increased risk of meningioma is observed in rare hereditary syndromes, mainly neurofibromatosis Type 1 and 2 (NF1 and NF2), and possibly in Turner's syndrome and Werner's syndrome.

Germline and somatic mutations in meningiomas: a significant increase in risk of meningiomas is associated with neurofibromatosis Type 2 disease through mutation of the *NF2* gene, and approximately 5% of individuals with schwannomatosis develop meningiomas, through mutation of the SWI/SNF chromatin remodeling complex subunit, SMARCB1.



NF2, Neurofibromatosis Type 2.

REVISION QUESTIONS

1. Which primary CNS tumour has the lowest sex ratio (male/female)?
2. It is recommended to prescribe hormone therapy to menopausal women with meningioma. True or false?
3. What are the two main histological types of primary CNS tumour associated with *NF2* gene mutation?

Summary: Epidemiology, pathogenesis and risk factors of brain tumours

- Primary CNS tumours are diverse histological entities with different causes
- Primary CNS tumours include malignant, benign and borderline tumours
- Meningiomas and gliomas are the two main histological types of primary CNS tumours
- Secondary CNS tumours (metastases) are more frequent than primary CNS tumours
- Glioblastoma is the most frequent glioma with a median age at diagnosis of 64 years
- Paediatric primary CNS tumour is the most frequent paediatric solid tumour
- Age, Karnofsky performance status, comorbidity, tumour growth rate, magnetic resonance imaging, histology and biology are important prognostic factors
- Symptomatology and QoL must be taken into account in the medical care management
- High-dose ionising radiation is the only unequivocal risk factor that was identified for glial and meningeal neoplasms
- Increased risk of glioma and meningioma is observed in rare hereditary syndromes

Further Reading

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