BRAIN TUMOURS **MEDICAL APPENDIX**

(Cerebral and intracranial tumours, including astrocytoma, glioblastoma, oligodendroglioma, ependymoma, medulloblastoma, meningioma, schwannoma, craniopharyngioma, choroid plexus tumour, neuronal tumour, pituitary adenoma and pineal tumours)

DEFINITION

1. Tumours of the brain may be benign or malignant, primary or secondary, multiple or single. This appendix will deal mainly with primary tumours arising within the brain or skull.

2. Primary intracranial tumours may be derived from the skull itself, from any of the structures lying within it, or from their tissue precursors. The classification of these tumours is complicated. For other tumour sites, likely effects and prognosis can be predicted from the tumour histology and, hence, degree of malignancy. The brain is housed within the skull, which restricts the room for tumour growth, and so the clinical impact of brain tumours relates to the site of the tumour and its closeness to vital structures.

3. In adults most tumours arise above the tentorium cerebelli, and they are generally histologically malignant. Childhood intracranial tumours are different in histological type and clinical behaviour, 70% of them arising below the tentorium. Malignant change and rapid growth may suddenly occur after years of slow progression of a small histologically benign lesion. Metastatic spread from primary cerebral tumours is rare.

CLASSIFICATION OF PRIMARY BRAIN TUMOURS

4. The majority of brain tumours are gliomas. In turn, they are subdivided.

Astrocytoma

5. These are the most common gliomas and primary intracranial tumours in both children and adults. They can occur at any age and affect men more frequently than women. They arise in the brain or spinal cord, most commonly in the white matter. Astrocytomas may undergo malignant change. When this occurs, it may be difficult to distinguish them histologically from glioblastoma multiforme.

Glioblastoma

6. Although usually considered a separate group, there is controversy as to whether this group of tumours is a distinct entity or a variant of astrocytoma. They affect men more than women, the peak incidence is in middle life and they are most frequently found in the cerebral white matter. The histology is complex and pathologists hold different views about the exact tumour origin. One group is of the opinion that they represent end-stage anaplastic gliomas, while the other considers that they arise *de novo* from primitive cells.

Oligodendroglioma

7. These are usually slow growing tumours of variable malignancy on histology, which occur most frequently in the cerebral hemispheres. They occur in adults, being most common in the fourth and fifth decades.

Ependymoma

8. These are predominantly tumours of childhood. They may occur in the cerebrum, particularly in the region of the fourth ventricle. They are often malignant.

Choroid plexus tumours

9. These also occur mainly in children and are of variable malignancy. About half of them are subtentorial and involve the third, fourth and lateral ventricles. Hydrocephalus is common.

Pineal gland tumours

10. The major significance of these tumours is their position. They are usually inaccessible operatively and their variable histology is often not established during life.

Medulloblastoma

11. These are highly malignant, usually arising in the roof of the fourth ventricle, with spread to the cerebellum. They are most common in the first decade of life, and are rare after childhood.

Schwannoma

12. These arise from the Schwann cells of the neural sheaths and are histologically benign. They usually arise on the 5th, 8th or 10th cranial nerves. They usually grow very slowly, but may produce pressure effects on the surrounding structures.

Meningioma

13. These are the **second largest group of adult primary intracranial tumours.** They may arise from any dural compartment or from the arachnoid covering the brain, and are most frequent close to the major dural venous sinus. They are mainly adult tumours, and may be multiple. The tumours are histologically benign but, incompletely removed, they may recur. They extend to involve the skull and produce a focal endostosis or exostosis. They are very slow growing and often clinically silent until very large.

Craniopharyngioma

14. These tumours are found in adults, but mainly in children. They are formed of epithelial cell remnants in the pituitary stalk. Their clinical features reflect their size and effect on surrounding structures. They involve the optic nerves or the third ventricle, with resultant hydrocephalus. They may expand into the pituitary fossa, causing hypopituitarism. Some are calcified and some cystic with cholesterol-rich fluid.

Pituitary adenoma

15. These are the commonest tumour of the pituitary gland and constitute about 10% of all primary cerebral neoplasms. They are of variable size and may be secretory or non-secretory. The non-secretory tumours may compress normal pituitary tissue, resulting in hypopituitarism. The secretory forms of tumour produce hormones leading to Cushing's syndrome, acromegaly or hyperprolactinaemia.

Other brain tumours

16. There are other less common primary cerebral neoplasms, which include neuronal and mixed glial tumours, colloid cysts, choroid plexus papillomas, ganglioneuromas, cholesteatomas, chordomas, haemangioblastomas, glomus jugulare tumours and intracranial sarcomas. Each of these rarities has its own characteristic features, including the age of onset, the degree of malignancy, whether it is solid or cystic, and its preferred intracranial site. Acoustic neuroma, the more localised tumour of the 8th cranial nerve, is the subject of a separate Medical Appendix.

Primary brain lymphoma

17. This is increasing in frequency in both AIDS and non-AIDS populations. This malignancy involves the brain, diffusely producing infiltrating, often multicentric, tumours. Primary brain lymphoma may involve the eye. The tumours derive from beta-lymphocytes and only rarely progress to systemic lymphoma.

CLINICAL MANIFESTATIONS

18. Intracranial tumours give rise to three symptom types:

    i. **symptoms of raised intracranial pressure**
    ii. **focal neurological effects** or
    iii. **epilepsy,** which may be generalised or focal.

    Systemic effects due to **inappropriate hormone production** may be present and there may be **meningeal irritation.**

19. The classic triad of symptoms of raised intracranial pressure in adults is headache, vomiting and drowsiness. The classic physical sign is papilloedema.

20. Focal neurological effects are legion and reflect the site of the tumour. Lesions in the cerebral hemispheres may produce mental and behavioural changes, weakness of the opposite side of the body, visual field defects and dysphasia. Brain stem lesions produce ataxia, visual problems and cranial nerve problems. Midbrain tumours may produce internuclear ocular palsies. Where specific cranial nerves are involved, the clinical features will reflect the loss of normal function.

AETIOLOGY OF BRAIN TUMOURS

21. Primary intracranial neoplasms represent 2-5% of all tumours. Despite considerable research, the precise aetiology of primary intracranial tumours remains unknown.

22. The highest rate of central nervous system tumours is found in females of Jewish origin born in Africa or Asia. Rates in Western countries are intermediate, and the lowest rates are found in Asia. The incidence of brain tumours in adults increases with age in many countries but, as with the observed international differences, it is difficult to know whether this is a real effect or merely a reflection of improved diagnosis.

23. Most brain tumours are sporadic but there is some evidence that the risk of developing an intracranial neoplasm of any histological type is marginally greater amongst those in whom there is a relative with a known cerebral tumour. In the phakomatoses - congenital disorders characterised by disordered growth of neuro-ectodermal tissue and giving rise to characteristic skin lesions - there is an increased incidence of cerebral tumours. Disorders involved include von Hippel Lindau Syndrome, von Recklinghausen's disease and tuberous sclerosis.

24. Studies investigating the causal relation of viruses, male and female sex hormones, smoking and alcohol to intracerebral tumours have been conflicting and no such associations have been accepted by general medical opinion.

25. Brain tumours have been induced in animals by chemical carcinogens, particularly alkylating agents used in cancer treatment. Occupational and chemical exposure and subsequent brain tumours in man have been intensively studied, particularly in Scandinavia, but no causal association has been confirmed.

26. Head trauma as a risk factor for adult brain tumour has been a controversial topic in medicine for over a century. Epidemiological studies have not demonstrated a direct causal relationship, but a recent international case control study has confirmed the findings of a previous smaller study and shows that there is a significant association between serious head injury requiring medical treatment and hospitalisation in males. This may be up to 15-24 years prior to the diagnosis of a meningioma. No such association is shown for other types of tumour or in females. It is important to note that the association is with significant head injury requiring acute medical treatment.

27. Ionising radiation exposure studies have shown a conclusive link with the development of intracerebral tumours of all histological types. This is so in both children and adults. Therapeutic irradiation of the nervous system for benign and malignant tumours or for non-neoplastic lesions may induce brain tumours. Neoplasms which are radiation-linked arise in the field of irradiation and have a long latent period. They are of varied histology, usually meningoma, glioma or sarcoma.

28. A link between brain tumours and electromagnetic radiation has been proposed. Epidemiological evidence is conflicting and the association is not presently accepted as causal. A major investigation on EMR and brain tumours is currently taking place in the United Kingdom.

29. Brain tumours have not been shown to be caused by climatic extremes, physical or mental stress, or lowered resistance arising from hardship or other diseases. There is no evidence that their progress is dependent on external factors, other than medical treatment.

CONCLUSION

30. Brain tumours exist as many different types and their classification is complicated. Apart from a possible genetic influence, increased incidence in some genetic brain disorders and a proven relationship to ionising radiation exposure, their aetiology is unknown.

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Annex A

Radiation dose

1. The first definition of a unit of radiation dose was made in 1928 by the International Congress of Radiology. The roentgen (R) was defined as that quantity of radiation which produces in 1 cm of air one unit of charge of either sign, thus defining a unit of exposure. Units of **absorbed dose**, the actual energy absorbed in the tissue being irradiated are now used. The radiation absorbed dose or **rad** is now cited in SI (Systeme Internationale) units – joules per kg – of absorbing material. The fundamental unit, 1 joule/kg, is 1 gray (1 Gy), equivalent to 100 rads (R).

2. Different radiation types have greater or lesser effect per unit dose, so they are all expressed relative to the effects of X-rays, i.e. a unit equivalent dose is used. To calculate the roentgen equivalent in man (**rem**), the absorbed radiation dose is multiplied by a radiation weighting factor, dependent on type and energy of the radiation. The current SI unit of equivalent dose is the **Sievert**. For X-rays and gamma rays the equivalent dose in sieverts and the absorbed radiation dose in grays are the same. The relationship between the different dose units is:-

   1 gray (Gy) = 1 joule/kg = 100 rads (R) = 100 rems (r) = 1 sievert (Sv) = 1,000 millisieverts (mSv) = 1,000,000 microsieverts (microSv). Typical doses of radiation include:

   Chest X-ray – 0.02 mSv
   Brain scan – 7 mSv
   Bone scan – 4 mSv
   Average annual UK dose from cosmic rays – 0.26 mSv
   Average annual UK dose from gamma rays – 0.35 mSv
   Average annual UK dose from natural background radiation – 2.2 mSv

3. **Effects of total body irradiation**

Equivalent dose (Sv)	**Effect**
Sub lethal to man 0.0001 (0.1 mSv)	Around 2 weeks' natural background radiation, no detectable effect
0.001 (1 mSv)	Around 6 months' natural background radiation, no detectable effect
0.01 (10 mSv)	No detectable effect
0.1 (100 mSv)	Minimal decrease in peripheral lymphocyte count, no clinical effect
1 (1000 mSv)	Mild acute radiation sickness in some individuals (nausea, possible vomiting), no acute deaths, early decrease in peripheral lymphocyte count, decrease in all WBC and platelets at 2-3 weeks, increase in late risk of leukaemia, solid tumours

Equivalent dose (Sv)	Effect
Lethal to man 10 (10,000 mSv)	Severe acute radiation sickness, severe vomiting, diarrhoea, death within 30 days of all exposed individuals. Severe depression of blood cell and platelet production, damage to gastrointestinal mucosa.
100 (100,000 mSv)	Immediate severe vomiting, disorientation, coma, death within hours
1000 (1,000,000 mSv)	Death of some micro-organisms, some insects within hours
10,000 (10,000,000 mSv)	Death of most bacteria, some viruses
100,000 (100,000,000 mSv)	Death of all living organisms, denaturation of proteins

Radiation dose limits

4. Since the days of Marie Curie it has been appreciated that ionising radiation exposure may be hazardous to health. Radiation dose limits were first recommended for ionising radiation exposure in 1928. The statutory limit on the amount of radiation to which the general public may be exposed in excess of natural background radiation and excluding medical exposure is set, from 1 January 2000, at 1 mSv per annum.

5. The most important source of man-made exposure is medical investigation which accounts for 90% of man-made exposure. Average natural background radiation is raised to 2.6 mSv by all man-made exposure. UK estimated exposure, excluding medical investigation, is 0.04 mSv. Other statutory limits include occupational dose limits. From 1 January 2000, these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers.

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