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A Review on Brain Tumour Incidence and Aetiology

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ABSTRACT

Brain tumors are common, requiring general medical providers to have a basic understanding of their diagnosis and management. The most prevalent brain tumors are intracranial metastases from systemic cancers, meningiomas, and gliomas, specifically, glioblastoma. Central nervous system metastases may occur anywhere along the neuroaxis, and require complex multidisciplinary care with neurosurgery, radiation oncology, and medical oncology. Meningiomas are tumors of the meninges, mostly benign and often managed by surgical resection, with radiation therapy and chemotherapy reserved for high-risk or refractory disease. Glioblastoma is the most common and aggressive malignant primary brain tumor, with a limited response to standard-of-care concurrent chemoradiation. This review addresses the specific contributions of nuclear medicine techniques, and especially positron emission tomography (PET), for diagnosis and management of brain tumors. F-Fluorodeoxyglucose PET has particular strengths in predicting prognosis and differentiating cerebral lymphoma from nonmalignant lesions. Amino acid tracers including C-methionine, F-fluoroethyltyrosine, and F-L-3,4-dihydroxyphenylalanine provide high sensitivity, which is most useful for detecting recurrent or residual gliomas, including most low-grade gliomas. They also play an increasing role for planning and monitoring of therapy. F-fluorothymidine can only be used in tumors with absent or broken blood–brain barrier and has potential for tumor grading and monitoring of therapy. Ligands for somatostatin receptors are of particular interest in pituitary adenomas and meningiomas. Tracers to image neovascularization, hypoxia, and phospholipid synthesis are under investigation for potential clinical use.

Keywords: Brain metastases**,** Brain tumor,Blood Brain Barrier**,** CT, MRI, Progenesis, Grading, FDG in CNS, Lymphomas

I. INTRODUCTION

Brain tumors share some features and challenges for diagnosis and therapy with tumors elsewhere in the body, but they also pose specific issues that are related to the unique properties of the organ they sit in. Most of the brain is separated from the blood by the blood– brain barrier (BBB) that exerts a much more restrictive control over substances that are allowed to pass (or may even be subject to facilitate transport) than most other organs. Thus, many tracers that easily reach tumors in the body would reach brain tumors only once the tumor caused a disruption of the BBB, for instance glioblastomas; when the tumor developed from intracranial tissues that do not have a BBB, for instance meningioma (derived from the meninges); or for brain metastasis (seeding from within the blood vessels). Thus, the disruption of the BBB, which can easily be detected on contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT), is regarded as the main diagnostic indicator for malignant gliomas, meningiomas, and brain metastases, as well as for some less frequent tumors without an intact BBB. As a consequence of the exclusion of all radiotracers that cannot pass the BBB from normal brain, there usually also is a good tumor-to-brain contrast for all tracers with these properties, which historically included ^{99m}Tc-pertechnetate and ^{68}Ga-diethylene triamine penta-acetic acid, and currently also fluorothymidine (FLT) and virtually all labeled macromolecules (although low-capacity slow-specific transfer by receptors has been observed for some). However, the excellent contrast may not indicate much more than the presence of BBB damage, which can readily be seen and even quantified by contrast-enhanced MRI. Therefore, much interest and effort has been invested into the development and evaluation of brain tumor tracers that do not depend on BBB damage, such as fluorodeoxyglucose (FDG) and labeled amino acids, because they are being transferred by large-capacity specific transporters across the intact BBB(1).

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It is important to grade tumors with respect to their malignancy. Although some tumor types, for example, meningiomas and neurinomas rarely become malignant, gliomas as the most frequent brain tumors exist in all 4 grades, usually classified internationally according to the World Health Organization (WHO) system.Grade 1 gliomas are rare and largely limited to childhood. Grade 2 gliomas (with subtypes astrocytoma and oligodendroglioma) occur in all ages with a peak in young adults. They show little cellular atypia and proliferation, but frequently infiltrate healthy surrounding brain, and, therefore, cannot be cured by surgery or radiotherapy. They represent a significant chronic medical problem and pose large uncertainties with regard to therapeutic decisions, which need to balance the imperative of saving intact functioning brain while trying to prevent those tumors from progression. More malignant gliomas are anaplastic (grade 3) or include gross cellular atypias and necroses, which characterize glioblastoma (grade 4). MRI and CT rely on BBB damage (frequent in grade 3 and 4, absent in grade 2) and morphologic appearance (eg, presence of necrosis, vascularity) for grading. Although this is regarded as largely sufficient in untreated gliomas, it becomes unreliable in treated tumors because BBB damage and necrosis also can result from formation of reactive tissue after therapy. In that situation, imaging methods that distinguish tumor from reactive non-neoplastic tissue will contribute significantly to clinical decision making. Contrast enhancement also cannot provide proper grading in brain tumors with a constitutive lack of BBB, such as meningiomas and lymphomas(2).

uptake in normal brain often makes the delineation of brain tumors difficult. Therefore, they need to be interpreted in conjunction, ideally by image fusion, with CT or MRI scans (Fig. 1). There have been studies suggesting that additional delayed imaging at 180 minutes or later after tracer injection can increase the contrast between malignant tumors with high FDG uptake and normal brain(3-5).

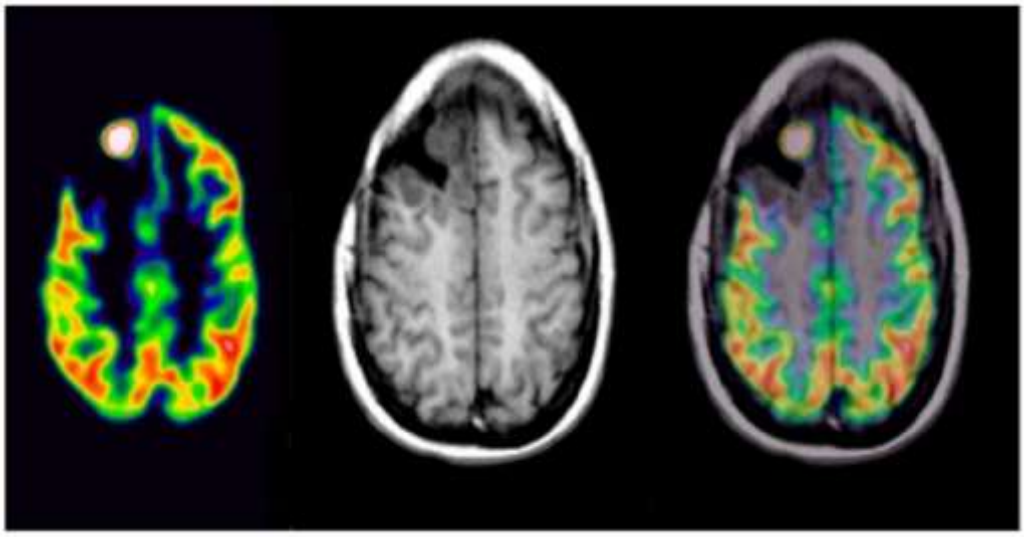

FIGURE 1 Left: Positron emission tomography (PET) scan with abnormality involving the right frontal lobe. Middle: Contrast magnetic resonance imaging (MRI) scan shows enhancement in the right frontal lobe. Right: There is a focal area of increased fluorodeoxyglucose (FDG) uptake involving the right frontal lobe consistent with a high-grade transformation and recurrence of tumor in the right frontal lobe 8 years after initial diagnosis and therapy. (Color version of figure is available online.)

Prognosis and GradinG

One of the first reports describing the utility of FDG in PET in the evaluation of brain tumors and the effect of radiation (RT) necrosis of the brain was published in 1982 by Patronas et al.[7] In this article, the authors described the problem of management of patients who have undergone previous therapy. The main issue is that therapy with RT produces RT necrosis. Once RT necrosis occurs, the associated clinical symptoms may become worse, and it becomes difficult to differentiate cerebral necrosis from recurrent viable tumor. The CT images demonstrate a mass of increasing size surrounded by edema with or without cavitation; after intravenous administration of contrast medium, enhancement of the lesion

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generally occurs. However, these clinical and CT findings are essentially indistinguishable from those encountered in some recurrent neoplasms. Using FDG-PET, the authors were able to establish a diagnosis of RT necrosis, later verified, in 10 of 95 patients referred for the purpose of differentiating tumor recurrence from necrosis(6). The critical FDG-PET feature was focal hypometabolism in the area of necrosis, which contrasted with the hypermetabolism associated with the residual recurrent tumor.

FDG in Central Nervous System (CNS) Opportunistic Infections and CNS Lymphoma

Establishing the diagnosis of a brain tumor can be difficult because many non-neoplastic neurological diseases can mimic brain neoplasms on neuroimaging or on histologic examination, including stroke, pyogenic abscess, toxoplasmosis, tuberculosis, cysticercosis, fungal infections, and sarcoidosis(7).

FDG-PET has shown some clinical advantage in assessing high-grade or LGG versus lymphoma or other opportunistic infections, such as histoplasmosis. Discrimination between lymphoma and toxoplasmosis is an issue most frequently arising in immunocompromised patients with acquired immunodeficiency syndrome. Most cerebral lymphomas have a high cell density and a high glucose metabolism, usually even higher than that of malignant gliomas and cerebral metastasis(8,9).

Imaging of Tumor Extent Biopsy and Treatment Planning

One of the most important aspects in the initial diagnosis of gliomas is the identification of tumor extension and the metabolically most active areas of the tumor. Representative tissue samples are important for histologic tumor diagnosis, prognostication, and treatment planning. The ability of MRI to show the most rapidly proliferating portions of the usually inhomogeneous gliomas is limited, particularly when the tumor does not take up contrast medium at CT or MRI. Multiple studies in which the radiological findings were compared with the histologic findings in tissue samples obtained by biopsy or open surgery have provided evidence that radiolabeled amino acids detect the solid mass of gliomas and metabolically active tumor areas more reliably than either CT or MRI(10-11) This helps to prevent the problem of nondiagnostic biopsies from nonspecifically altered tissue and to plan surgical resection. A recent study demonstrated that integrating C-MET-PET into the image-guided resection of HGG provided a final target contour different from that obtained with MRI alone in approximately 80% of the procedures(12).

Imaging Brain Tumors in Children

the histologic subtypes of brain tumors in children differ considerably from that in adults. Only few mainly retrospective studies have been performed in children with brain tumors. In children, the determination of tumor grade with amino acids seems to be even less reliable than in adults. A broad overlap of amino acid uptake is observed in low-grade and high-grade tumors. Similar to glucose metabolism, amino acid uptake may be high in low-grade tumors such as pilocytic astrocytomas and gangliogliomas; uptake may be relatively low in the highly aggressive medulloblastomas (WHO grade IV), a common diagnosis in infratentorial brain tumors. The potential of amino acids to determine the site of stereotactic biopsy or for image-guided surgical resection of infiltrative low-grade brain tumors in children has been reported. The presence of amino acid uptake after surgery indicates residual tumor in case of ambiguous findings in early postoperative MRI(13).

Radiopharmaceuticals

single- and coincidence-photon– emitting radiopharmaceuticals have been used for diagnosing, grading, and monitoring brain tumors.

Risk Factors

Current thinking suggests that brain tumours develop as a consequence of accumulated genetic alterations that permit cells to evade normal regulatory mechanisms and destruction by the immune system. These alterations may be in part or wholly inherited but any agents—chemical, physical or biological—that damage DNA are possible neurocarcinogens. Investigations of the causes of brain tumours should ideally address the simultaneous influence of both genetic factors and environmental exposures(14).

Genetics

Genetic predisposition to developing brain tumours is associated with certain inherited syndromes such as tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, and syndromes involving adenomatous polyps. These syndromes account for 1–2% of all tumours. The Li-Fraumeni cancer family syndrome is also associated with a predisposition to brain tumours and specifically with mutations in the TP53 gene. Mutations in constitutional (that is, non-tumour tissue) TP53

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have been linked to patients with gliomas. Future work on causality should be able to account for possible interactions between known genetic predisposition in the investigation of environmental risk factors.

Familial aggregations of brain tumours occurring in different generations and sibships occur very rarely and the patterns of inheritance are inconsistent. In these situations common environmental exposures cannot be excluded as an explanation. Overall, it appears that only a very small proportion of brain tumours can be attributed to the effect of inherited predisposition.

Common variations in the structure of specific genes are known to be associated with basic cellular metabolic processes such as oxidation, detoxification, DNA stability and repair, and immune functioning. Such genetic polymorphisms may well be associated with the development of brain tumours in the presence or absence of environmental carcinogens. However, the limited findings available so far have failed to consistently identify any specific polymorphisms, but this remains a potentially fruitful line of research and future large sample studies are needed(15)

Chemicals

N-nitroso compounds are found in the environment but the most common source of human exposure is through foods, with vegetables and cured meats being major sources. Certain alkylating agents, such as ethyl and methyl nitrosurea, are known transplacental carcinogens, particularly for brain tumours in rats. Their ability to cross the blood–brain barrier and their mutagenic potential makes them ideal candidates as initiators in the carcinogenic process. In humans, dietary and environmental N-nitroso compounds have been studied as potential brain tumour carcinogens along with the potentially protective effect of consuming antioxidants. The sources of antioxidants include fresh fruit and vegetables, supplements, and endogenous metabolic pathways. Attributing the cause of brain tumours to these compounds or other dietary factors such as vitamin supplements has received mixed support in the published literature. Dietary assessment is fraught with problems and it may be that the ingestion of potentially toxic compounds is offset by the ingestion of antioxidants which promote DNA repair. Nitrate levels in drinking water have also been investigated but no consistent associations found.

The low calorie sweetener aspartame has been commonly used in a number of food products for over 15 years. It has been suggested to be involved in the aetiology of some brain tumours based principally on the results of laboratory experiments. The biological basis for any influence which aspartame could have on the risk of developing a brain tumour is unclear.

Tobacco smoke is carcinogenic but many constituents do not pass the blood–brain barrier. Smoking does not appear to be strongly linked to brain tumours either in adults who smoke themselves or via maternal smoking in pregnancy. A similar lack of association is seen for alcohol consumption.

Various other chemicals have received attention. Hair dyes and hair sprays were implicated as risk factors for brain tumours in some early epidemiological studies but the observations remain unconfirmed. Further inconsistent reports have linked childhood brain tumours to pesticide exposure, traffic pollution, and parental occupations. The possibility of fathers' sperm being damaged and the developing fetus being affected by parental occupation and the development of childhood brain tumours has been extensively studied, but few conclusions have been drawn. A recent large scale case–control study of childhood cancers in the UK failed to show any significant associations between brain tumours and the occupations of either mothers during pregnancy or fathers around the time of conception.

In the working population many jobs in various industries involve exposure to carcinogenic or neurotoxic compounds including organic solvents, polycyclic aromatic hydrocarbons, lubricating oils, and phenols and the question has been frequently asked as to whether such exposure is related to brain tumours. Despite numerous studies no consistent risks have been isolated for any chemical or group of workers apart from those in the petrochemical and oil industry. In these circumstances no specific chemical has been identified and the possibility of multiple exposures has to be considered(16).

Head Trauma and Injury

Patients with brain tumours inevitably recall occurrences of trauma or injury to the head with greater frequency than the general population, and studies of patients' reports are therefore subject to "recall bias". Some epidemiological investigations of the relation between head trauma/injury and the subsequent development of a tumour have attempted to overcome this by examining medical records, but these mainly fail to demonstrate any relation. The inevitable pitfall of recall bias as an explanation of a raised risk renders

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most work in this area virtually impossible to interpret(16).

II. CONCLUSION

Brain tumours in adults are a rare disease from which survival is generally poor compared to many other cancers. Reports of rising trends need to be cautiously interpreted as they may well be explained by changes in diagnostic and clinical practice. In childhood a different profile of tumour types is present and survival has improved over recent years and is higher than in adults. Apart from genetic predisposition, the most well established environmental risk factor for brain tumours is exposure to high doses of ionising radiation. Research into infections and immune factors may prove a fruitful avenue of investigation.

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