Role Of Brain SPECT Scan and MRI – Spectroscopy in Evaluation Of Post therapy residual or recurrence Of Primary brain tumors

Thesis

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ABSTRACT

Introduction: The differentiation between recurrent tumor progression and radiation therapy effects in subject previously treated for glioma is problematic Computed tomography and magnetic resonance imaging offer imperfect discrimination of tumor viability and radionecrosis. Both brain SPECT and proton MR spectroscopy may be useful to differentiate between tumor recurrence and radiation necrosis **The aim of this study** was to compare 99mTc-penta (v)DMSA brain SPECT versus proton magnetic resonance spectroscopy (1H-MRS) findings for detection of recurrent glioma in 24 patients after radiation therapy. **METHODS:** Both exams were performed on 24 glioma patients, previously operated upon and treated with radiotherapy, SPECT images were acquired 3 hours after 40 MBq (20 mci) of Tc99m DMSA administration with a dual-head gamma camera. T/N uptake ratio was calculated between a tumor ROI (T) and a normal mirror symmetric ROI (N). 1H-MRS was performed using a 1.5 T system equipped with a spectroscopy package. SPECT and 1H-MRS data were compared with pathology after new surgery or with follow-up. **RESULTS:** SPECT and 1H-MRS showed recurrence in 9 patients (confirmed by biopsy or follow up) and both were negative in 6. SPECT and 1H-MRS disagreed in 9 cases of recurrence (7diagnosed by as positive viable tumor as brain SPECT, 2 by 1H-MRS). SPECT and 1H-MRS sensitivity in detecting recurrence as compared with surgical biopsy or follow up was 88.8%,61.1% respectively with accuracy 91.6%, 45.8.% respectively

CONCLUSIONS Brain SPECT had higher detection in differentiating tumor recurrence and post radiation changes as compared to 1H-MRS and in the follow-up of treated glioma**.**

Key WORDS :

Comparison between 99mTc-(v)DMSA brain SPECT and proton magnetic resonance spectroscopy (1H-MRS) in assessment of glioma recurrence after radiotherapy

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LIST OF ABBREVIATION

ATPase	**Adenosine triphosphatase**
BBB	**Blood brain barrier**
CNS	**Central nervous system**
CBF	**Cerebral blood Flow**
CBV	**Cerebral blood Volume**
CSI	**Chemical Shift imaging**
CHo	**Choline**
CT	**Computed tomography**
Cr	**Creatine**
CTA	**CT angiography**
CTV	**CT venography**
DTPA	**Diethylene triamine Penta acetic acid**
DWI	**Diffusion weighted imaging**
DMSA	**Dimercaptosuccinic acid**
EMF	**Electromagnetic fieid**
FLAIR	**Fluid attenuated inversion recovery**
FDG	**Fluroro-2-deoxy-D-glucose**
FMRI	**Functional MRI**
KeV	**Kilo electron Volt**
MRI	**Magnetic resonance imaging**
MRS	**Magnetic resonance Spectroscopy**
MTT	**Mean transit time**
MCT	**Medullary carcinoma of the thyroid**
MBq	**Mega Becquerel**
MIBI	**Methoxy isobutyl isonitrile**
NAA	**N- acetylaspartate**
NCI	**National Cancer Institute**
PET	**Positron emission tomography**
rCBV	**Regional cerebral blood volume**
SPECT	**Single photon emission computed tomography**
SVS	**Single Voxel spectroscopy**
(TL)201	**Thallium-201**

LIST OF TABLE

Introduction

The major clinical challenge in the follow-up of glioma following treatment is to diagnose of early tumor recurrence. Management of glioma strictly depends on the grade of malignancy. High-grade astrocytomas tend to relapse rapidly after therapy, whereas low-grade gliomas show slow progression in the grade of malignancy. In the latter patients, confirmation of recurrence and determination of the current tumor grade contribute to the rapid administration of appropriate adjuvant therapy that may result in a fundamental improvement in patients' individual prognosis. However, the differential diagnosis between recurrent glioma and post therapeutic gliosis poses particular problems *(Hein et al, 2004).*

Computed tomography (CT) and magnetic resonance imaging (MRI), the two diagnostic techniques most widely used for morphologic imaging of tumors and for monitoring therapeutic response, frequently fail in differentiating recurrence or regrowth of residual tumor from other lesions. Several studies have demonstrated that CT and MRI cannot reliably differentiate viable tumor tissue from tumor-associated edema, postoperative changes, or radiation necrosis *(Hein et al, 2004).*

Metabolic imaging techniques such as positron emission tomography (PET) , single photon emission computed tomography (SPECT) and MR spectroscopy have been proposed as alternative modalities for detecting tumor recurrence on the basis of the hypothesis that malignant neoplasms have biologic characteristics that are distinct from those of normal and radiation-damaged brains *(Pauleit et al, 2004).*

Over the last two decades the large volume of research involving various brain tracers has shed invaluable light on the pathophysiology of cerebral neoplasms. Yet the question remains as to how best to incorporate this newly acquired insight into the clinical context. Thallium is the most studied radiotracer with the longest track record. Many, but not all studies show a relationship between ^{201}Tl uptake and tumor grade. Due to the overlap between tumor uptake and histologic grades, ^{201}Tl is mainly used as a prognostic tool in brain tumor patients because It help in differentiating a high-grade tumor recurrence from radiation necrosis *(moustafa et al, 1994).*

99m Tc MIBI and 99m Tc DMSA is theoretically a better imaging agent than ^{201}Tl but it has not convincingly been shown to differentiate tumors according to grade. Tc99m has higher energy 140 Kev and a shorter half life 6 hour which allow IV injection of higher doses 5 to 10 times more than Tl 201. Therefore the images are of higher quality and better resolution. Currently, 99m Tc DMSA is better in evaluation of mid line brain tumor *(El-Rafiee et al, 2003).*

MR Spectroscopy provides information non-invasively on tumor biochemistry. The MRS data are seen to provide unique information. When combined with high-quality anatomical MR images have implications for defining tumor type and grade, directing biopsy or surgical resection, planning focal radiation or biological therapies, and understanding the mechanisms of success and failure of new treatments. Single voxel proton MR spectroscopy has been applied for characterizing the metabolic. Signatures of brain tumors for some time. There is strong

evidence for a reduction in *N*-acetylaspartate and increase in choline containing compounds in tumor *(Law et al, 2003).*

Although single voxel proton MRS is a relatively rapid method for obtaining information about the metabolism, it does not address spatial heterogeneity and is unable to contribute to defining the spatial extent of the lesion. These factors are particularly important for planning focal treatments such as radiation and surgical resection and for following response to therapy *(Vos et al, 2003)*

AIM OF THE WORK

To evaluate the diagnostic utility of brain SPECT as compared to MR spectroscopy in differentiating viable tumor tissue from postoperative radiation necrosis or chemotherapy changes.

Pathology of brain tumors

Blood Brain Barrier

Understanding the pathologic phenomena accompanying brain tumors requires an appreciable knowledge of the blood brain barrier (BBB). This a dynamic interface between the brain and the body, which regulates which substances are allowed to enter the brain parenchyma. The BBB is made of specialized endothelial cells and their surrounding astrocytic foot processes. The endothelial cells in the brain vasculature are non-fenestrated, lack intercellular clefts, and pinocytic vesicles. Furthermore, they contain much more mitochondria than normal systemic endothelial cells, and this is to help energy supply to the multiple energy-dependent transporters in the BBB. In general, though, the more lipid soluble a substance, the easier it passes through the blood brain barrier (fig (1) *(costa, 1994)*

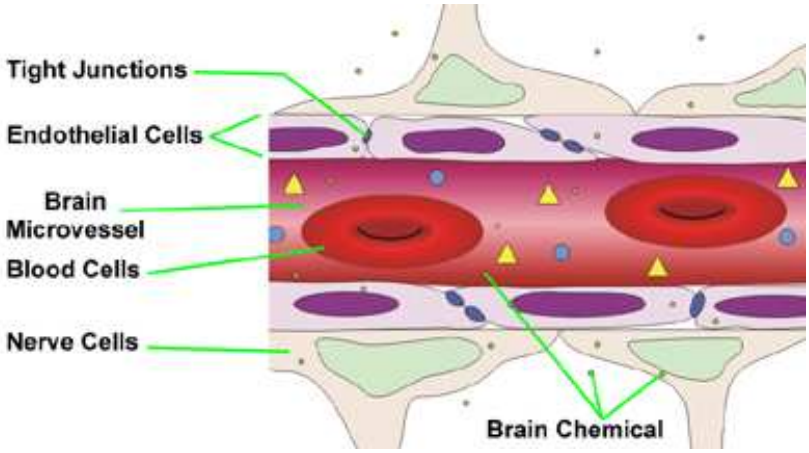

Fig (1) Blood brain barrier and the tight junction between the Endothelial cells

Brain tumors alter the permeability of the blood brain barrier by opening tight junction between endothelial cells, inducing capillary fenestrations, and increasing pinocytic vesicles. Furthermore, astrocytic foot processes seem to be absent where tumor has disrupted the BBB. Disruption of blood brain barrier induces cerebral edema, increase intracranial pressure and generate seizures, *(Dennis, 1997)*

Brain Edema

Brain edema is one of the most important factors leading to morbidity and mortality associated with brain tumors. When steroid therapy was introduced in the 1960's, post-operative mortality for brain tumor decreased 10 fold. *Pappius (, 1993)* defined brain edema is an increase in brain volume resulting from increased sodium and water content. Brain edema may contribute to headache, focal neurological signs and depressed level of consciousness. There are three main types of edema.

1. Vasogenic 2.cytotoxic 3.hydrocephalic or interstitial *(Thapar et al,2001)*

Vasogenic is the most common type of edema associated with brain tumors and results from local disruption of the BBB. This leads to extravasation of protein-rich filtrate of plasma its accumulation and permeation within extra cellular space of the brain constitutes of edema. This disruption results from loosening of the tight junctions between endothelial cells, and the neoformation of pinocytic vesicles. Once the barrier is breached, hydrostatic and osmotic forces work together to extravasate intravascular fluid. Once extravasated, fluid is retained outside the vasculature, mostly in the white matter of the brain within the bundles of myelinated axons. This is because axons run in parralel bundles of fibres with loose extracellular space, as opposed to gray matter, which has high

cell density and is enmeshed in network of connecting fibres that offer high resistance to the edema. By definition, this edema is confined to the extracellular space fig (2) demonstrate vasogenic edema from high grade neoplasm in right parietal lobe *(Thapar et al, 2001)*.

On the other hand, **cytotoxic** edema is characterized by cell swelling, with a parallel reduction in the volume of fluid in the extracellular space. This type of edema is seen in most commonly with cerebral ischemia, resulting from occlusion or hemorrhage of cerebral vasculature. The primary mechanism is loss of ATP driving the sodium-potassium (ATPase pump) due to local hypoxia resulting from ischemia. Thus sodium accumulates in the intracellular space, and created an osmotic gradient for water to enter the cells. In comparison to the Vasogenic edema where protein rich filtrate, this edema consists of sodium and water. By definition, the BBB is still intact, at least initially. Both gray matter and white matter are affected by this type of edema as both become swollen. As a rule this type of edema is not associated with tumors. However, in the case of compression of microcirculation, or with herniation syndromes, which compress major cerebral arteries, this type of edema can occur *(Rubin et al, 1999)*.

The Interstitial or hydrocephalic edema occurs when there is an accumulation of extracellular fluid in the setting of hydrocephalus. This is best demonstrated when there is an obstructive hydrocephalus, which creates a hydrostatic gradient between the ventricles and the brain parenchyma proximal to the obstruction. That result is transependymal movement of CSF into the intracellular space, most evident in the peri-ventricular white matter. This type of edema most accompanies posterior fossa tumors that obstruct the 4^{th} ventricle, or intraventricular tumors that increase intraventricular hydrostatic pressure *(Thapar et al, 2001)***.**

Risk Factors of brain tumors

There are only a few well-established risk factors for brain tumors. People receiving radiotherapy (high-dose ionizing radiation) to the head during childhood are at increased risk for developing brain tumors, as are people with certain rare genetic disorders such as neurofibromatosis .The molecular and health effects in humans of low frequency, non-ionizing radiation such as that produced by electrical appliances, power lines, or cell phones show no consistent association. The available data on electromagnetic fields (EMF) produced by electrical appliances or electric power lines are insufficient to support the conclusion that low-frequency fields cause cancer. Similarly, early reports on the use of cell phones for five years or less do not show an association with brain tumor risk .There has been several epidemiologic studies suggesting that nervous system cancers may be related to a variety of environmental exposures, including N-nitroso compounds (e.g., nitrosamides or nitrosamines) and some solvents. In addition, an excess risk has been suggested among workers in certain industries such as the manufacture of synthetic rubber and polyvinyl chloride, the refining of crude oil, the production of petroleum-based chemicals, and the manufacture of pharmaceuticals. Certain professional groups, as well, such as electrical workers, chemists, embalmers and pathologists have been reported to have higher than expected brain cancer rates. However, aside from the small percentage of brain tumor cases that can be linked to exposure to high-dose ionizing radiation or to certain inherited genetic alterations, few specific risk factors have been convincingly linked to brain tumors *(Ljubimova et al, 2001).*

The incidence of a primary brain tumor is higher than that of a metastasis. Incidence of a primary tumor of the central nervous system (CNS) is approximately 15 per 100,000 persons (i.e., each year, for every 100,000 people in the, approximately 15 people will be diagnosed with a somewhere between 40,000 to 50,000 people The lifetime chance of developing a primary CNS tumor is approximately 1 in 200 (slightly higher in men than women) CNS tumors are the leading cause of cancer-related deaths in children and teenagers, and the second leading cause of cancer-related deaths in males aged 20-40 years. 40% of primary CNS tumors are "gliomas" (e.g., astrocytoma, oligodendroglioma, ependymoma, mixed glioma)while 80% of malignant CNS tumors are gliomas For every 100 persons diagnosed with CNS glioma, approximately (50%) will have the most malignant form (glioblastoma multiform) at the time of diagnosis *(Davis et al,1999).*

The incidence of brain tumor in Egypt according to National Cancer Institute (NCI) statistics were estimated that in 2005, there were a total of 18,500 new cases of brain and other nervous system tumors diagnosed - 10,620 males and 7,880 females. The estimated number of deaths was 12,760, of which 7,280 were males and 5,480 were females. From 1998-2002, the median age at diagnosis for cancer of the brain and central nervous system was age 55 *(El-Bolkainy et al,2005).*

The WHO Classification of Tumors affecting the Central Nervous System (CNS) *Kleihues et al, (2000)*

The WHO grading of CNS tumors establishes a malignancy scale based on histologic features of the tumor. The histologic grades are as follows:

Grade I includes lesions with low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone.

Grade II includes lesions that are generally infiltrating and low in mitotic activity but recur. Some tumor types tend to progress to higher grades of malignancy.

Grade III includes lesions with histologic evidence of malignancy, generally in the form of mitotic activity, clearly expressed infiltrative capabilities and anaplasia.

Grade IV includes lesions that are mitotically active, necrosis-prone, and generally associated with a rapid preoperative and postoperative evolution of disease. *(Kleihues et al, 2000)*

Classification.

●Neuroepithelial tumors.

I. Astrocytic tumors.

a. Pilocytic astrocytoma.

b. Diffuse astrocytoma (including fibrillary, protoplasmic, and gemistocytic).

c. Anaplastic astrocytoma.

d. Glioblastoma (including giant cell glioblastoma, and gliosarcoma).

e. Pleomorphic xanthoastrocytoma.

f. Subependymal giant cell astrocytoma.

II. Oligodendroglial tumors.

a. Oligodendroglioma.

b. Anaplastic oligodendroglioma.

III. Mixed gliomas.

a. Oligoastrocytoma.

b. Anaplastic oligoastrocytoma.

IV. Ependymal tumors.

a. Myxopapillary ependymoma.

b. Subependymoma.

c. Ependymoma (including cellular, papillary, clear cell, and tanycytic).

d. Anaplastic ependymoma.

V. Neuroepithelial tumors of uncertain origin.

a. Astroblastoma.

b. Chordoid glioma of the third ventricle.