Radioactive oxygen ^{15}O studies in cerebral neoplasms¹

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Summary

Methods of diagnosis and anatomical localization of cerebral neoplasms have reached a high level of efficiency. A new method of studying cerebral circulation and metabolism by a simple noninvasive technique of steady-state imaging during the inhalation of radioactive oxygen and radioactive oxygen-labelled CO_2 is described. The results of preliminary studies of a group of cerebral neoplasms of various histological types are presented and the implications discussed.

Introduction

Most *in vivo* studies of cerebral neoplasms are concerned with the diagnosis, localization and extent of spread of the neoplastic process. The radioactive oxygen studies reported here differ in their aim, which has been to determine whether the simple noninvasive inhalation technique, first described by Jones, Chesler & Ter-Pogossian (1976), can give useful information regarding the pathological physiology of the neoplasm and its effect on circulation and oxygen utilization of the brain as a whole. Subsequent to this initial report of the method, its use in a variety of neurological conditions (Lenzi, Jones, McKenzie, Buckingham *et al.* 1978) and its use in cerebral neoplasms (Jones, McKenzie *et al.* 1976, McKenzie *et al.* 1977) has been described.

Briefly, the method depends on the high utilization of oxygen by cerebral tissue. The inhaled radioactive oxygen is delivered to the tissue by the blood stream and the quantity utilized by the cells depends on: (1) the perfusion of the tissue by the blood delivering the radioactive oxygen; (2) the ability of the cells to utilize the oxygen delivered, i.e. the metabolic activity of the tissue. Oxygen takes part in one biochemical reaction:

Thus all the oxygen utilized becomes water of metabolism, and the signal coming from any part of the brain depends on the concentration of the isotope in the metabolic water. The contribution from the oxygen in the blood stream is small. The concentration of oxygen in metabolic water is given by the following formula:

$$\text{H}_2 {}^{15}\text{O met} = \frac{\text{Ca} - \text{Cv}}{\text{Cv}} \cdot \text{Ca}^* \cdot \frac{(\text{F})}{(\lambda + \text{F}/\text{V})}$$

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where Ca and Ca^* are the arterial concentrations of stable and radioactive oxygen respectively; C_v is the venous oxygen concentration and F the flow rate; λ is the radioactive decay constant for ^{15}O and F/V the rate of washout of the tracer from a volume of tissue V . It can be seen that the relationship is linear with respect to tissue oxygen extraction, but is not linear with respect to flow (Jones, Chesler & Ter-Pogossian 1976).

As the utilization of oxygen is affected by the blood flow, it is clearly desirable to be able to examine the blood flow term in this expression separately. This can be done by using $^{15}O_2$ in the form of $C^{15}O_2$. When carbon dioxide is inhaled it is immediately converted into water under the influence of carbonic anhydrase (West & Dollery 1962). This radioactive water enters the circulation and, being freely diffusible, can pass into the extracellular and intracellular fluid compartments without having to be utilized by the cellular cytochrome system. The signal given from this water by perfusion is given by the following formula:

$$H_2^{15}O \text{ circ} = \frac{(F)}{(F/V + \lambda)} C$$

where C equals the arterial concentrations of $H_2^{15}O$. The signal is not linear with respect to flow but has a certain sensitivity particularly to reductions in blood flow, and hence has been used as a means of assessing regional cerebral blood flow.

Materials and methods

Fourteen patients with cerebral neoplasms have been studied by this regional cerebral blood flow/oxygen utilization method: one recurrent medulloblastoma, 3 meningiomas, 9 astrocytomas and one microglioma. The technique involved the on-line use of the isotope ^{15}O produced by the MRC Cyclotron Unit at Hammersmith Hospital (Mr P D Buckingham & Mr J C Clark). ^{15}O is the longest-lived isotope of oxygen, having a half life of 2.1 minutes and the gas is piped 700 ft (212.8 m) to the clinical area where it is administered to the patient by continuous inhalation through a face mask. The majority of gas inhaled by the patient is room air into which is introduced the radioactive isotope oxygen 15 at the rate of 1.5 mCi/min and radioactive CO_2 at the rate of 0.75 mCi/min. The build up to a steady state takes six minutes and imaging is then carried out under the resulting condition of dynamic equilibrium for a period of four minutes. The oxygen $^{15}O_2$ and $C^{15}O_2$ studies are carried out sequentially without the patient moving. The imaging is carried out with an Anger gamma camera fitted with a $4\frac{1}{2}$ in (11.43 cm) lead collimator (Westerman & Glass 1968) to improve its performance in recording the 511 Kev annihilation gamma rays of the positron emitting isotope. The data is recorded and stored in a Hewlett Packard (H P2100A) computer and subsequently displayed to produce analogue photographs on 64×64 numerical matrix from which semiquantitative data can be obtained and analysed.

Results

Normal brain: Figure 1 shows a normal subject examined using the isotope in three chemical forms. The definition is rather better than in some subsequent studies and in this case it was obtained with a Brownell positron camera (Brownell & Burnham 1972) using coincidence counting. There is a brain-shaped outline and a slight difference in the image produced by the inhalation of radioactive oxygen compared with that produced with radioactive carbon dioxide. The central area in the oxygen image shows less activity in the central region corresponding to the central white matter. A third image was produced using the isotope in the form of carbon monoxide; this labels red cells only and the signal depends on the quantity of blood present in any part, which reflects quantity present in the venous sinuses surrounding the brain. This image is useful as it is clearly larger than those with oxygen and carbon dioxide, and therefore shows that the latter images are from the brain and not from the whole head.

Figure 1. Normal brain studied with radioactive oxygen in the form of $^{15}\text{O}_2$, C^{15}O_2 and C^{15}O

Meningioma: Three cases were studied and the same results were seen in all of them. In one of these cases, the position of the tumour is shown by cerebral angiography (Figure 2). In the C^{15}O_2 image (Figure 3) there is an area of increased uptake corresponding to this tumour position, but in the $^{15}\text{O}_2$ image this is absent. The interpretation of this is that the tumour and its surrounding brain have a high blood flow, while the metabolic activity as shown by the $^{15}\text{O}_2$ image is low. There is therefore an element of regional luxury perfusion (Lassen 1966).

Medulloblastoma: One case of a large frontal recurrence of a medulloblastoma is shown by EMI scanning (Figure 4). The $^{15}\text{O}_2$ image (Figure 5) shows an area of increased activity in the region of the tumour which is more marked than in the C^{15}O_2 study. In this case there is an increased extraction of oxygen by the tumour as compared with normal brain in this region. In this respect, it may be of interest that this particular medulloblastoma showed histological differentiation towards oligodendroglioma, a tumour which, in *in vitro* studies (Allen 1972), has been shown to have a high oxygen consumption.

After irradiating the tumour the image changed and the high oxygen consumption in the frontal area was no longer present. On EMI scan, considerable shrinkage of the neoplasm was seen, and this residual mass was removed and the patient remained well for a time. However, subsequently he developed recurrent signs of a frontal lobe lesion and an EMI scan once again showed a space-occupying lesion. Unfortunately, we did not have an opportunity to study this patient at this stage with $^{15}\text{O}_2$. Had we done so, the result would have been clearly different from the previous recurrence. Exploration showed the mass to be a subdural haematoma.

Astrocytomas: This group of 9 patients did not show such consistent features as the meningiomas or the medulloblastoma. Abnormalities were seen in all cases and in the majority

Figure 2. Carotid angiogram showing position of a parasagittal meningioma. (By courtesy of Dr H Shawdon, Central Middlesex Hospital)

Figure 3. Radioactive oxygen studies with the isotope in the form of $C^{15}O_2$ showing area of high uptake corresponding to the position of the tumour, and absence of this area of high uptake in the study using $^{15}O_2$

Figure 4. EMI scan of a massive frontal recurrence of a medulloblastoma. (By courtesy of Dr J Ambrose, Atkinson Morley Hospital)

the uptake in the tumour area was decreased more in the metabolic $^{15}\text{O}_2$ image than in the perfusion C^{15}O_2 image (Figure 6). This may not be true in all gliomas. Alpert *et al.* (1977) reported a case in which the perfusion through the tumour area was increased similar to the meningioma cases in this series.

Effects of therapy

The effects of therapy have been studied in some astrocytoma patients. The results have been difficult to interpret and to correlate with clinical findings. One case, a microglioma, an extremely radiosensitive neoplasm, was studied (Figure 7). Prior to therapy the patient had a well-marked right hemianopia and evidence of right parietal lobe involvement. The first study was done shortly after starting radiotherapy and at weekly intervals thereafter. The defect in the parieto-occipital region in the first scan is less marked in the second, and the metabolism in the second scan is more affected than the perfusion. The third study shows continued overall improvement.

Semiquantitative studies

From the data stored in the computer a 64×64 numerical matrix is obtained and from this contour maps are drawn out by hand to give the different levels of oxygen consumption and perfusion. By normalizing the counts in various parts of the brain with respect to the area of highest activity, which in these studies is in the anterior temporal region, figures representing the relative perfusion of six areas and relative metabolism of these areas were obtained (Figure 8). These indices have been termed the perfusion ratio (PR) and the metabolic ratio (MR) respectively. By dividing the metabolic ratio by the perfusion ratio, a further index – the oxygen extraction ratio (OER) – can be calculated. This index has the theoretical advantage of being the ratio of the two other ratios, thus being relatively independent of the geometrical

Figure 5. Radioactive oxygen studies of the case in Figure 4 showing the increased uptake in the tumour area with ¹⁵O₂ and the absence of increased uptake with C¹⁵O₂. After treatment the difference is no longer present

Figure 6. Cystic astrocytoma showing reduction in uptake of C¹⁵O₂ and ¹⁵O₂, the reduction being greater for ¹⁵O₂

Figure 7. Microglioma undergoing treatment by radiotherapy. Reduction in the uptake in both the $^{15}O_2$ and $C^{15}O_2$ studies was most marked in the study of 11.11.77, with progressive reduction in abnormality on 17.11.77 and 24.11.77

Figure 8. Normal distribution of radioactivity of the isotope in the forms of $C^{15}O_2$ and $^{15}O_2$. (Reproduced from Lenzi, Jones, McKenzie, Buckingham *et al.* 1978, by kind permission)

configuration of the brain. An example of a study of this type in an astrocytoma case is shown in Figure 9. It shows clearly that not only is the perfusion and metabolism abnormal in the tumour area but, comparing the other parts of the brain, the difference between the indices with those in the normal brain are quite marked. This widespread disturbance of metabolism and circulation is in keeping with the findings of Endo *et al.* (1977).

While the inaccuracies of this semiquantitative method are freely admitted, it does provide the opportunity to analyse the patients as a group. For the neoplasm patients the indices have been calculated, and the relationship between blood flow and metabolism is shown in Figure 10. The meningioma cases had a blood flow higher than normal in the tumour area and a lowered metabolism. The astrocytomas showed differences and generally the blood flow and metabolism were both lowered – the degree varying from case to case. The one medulloblastoma showed above-normal metabolism compared with circulation.

Discussion

These studies have been useful in two respects. First, in testing a new method of investigation, the well-defined gross lesions of cerebral neoplasms have provided a confirmation that the method is able to demonstrate the physiological abnormalities expected, and thus provides a background for assessing studies in which the anatomical lesions are less in evidence (Lenzi, Jones, Reid & Moss 1977; Lenzi, Jones, Thomas & Moss 1977; Lenzi, Jones, McKenzie & Moss 1978; Pinching *et al.* 1978). Secondly, they have provided some information regarding the pathological physiology of cerebral neoplasms and their response to treatment. Clearly, the method as described has severe limitations, in particular the two-dimensional image provided by the Anger camera. Three-dimensional imaging and absolute values for perfusion and metabolism can be obtained by the use of emission transverse tomography with a device such as the new Ortec ECAT 8. Apart from the theoretical interest of such studies, the results may have important implications for treatment. While transmission transverse tomography is highly efficient in showing gross spread, it is unable to demonstrate microscopic infiltration

Figure 9. Abnormal distribution of radioactivity in a case of astrocytoma (hatched area), cf Figure 8

Figure 10. Comparison between the perfusion ratio (PR), metabolic ratio (MR) and oxygen extraction ratio (OER) in the various types of cerebral neoplasm

and gives no information regarding the physiological aspect of the tumour, such as the degree of oxygenation of the mass. Physiological radioisotope emission studies of this type would enable a complete anatomical physiological reconstruction of the tumour to be made. With this information available a rational approach to treatment is possible.

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