The first use of a radioactive substance for detecting brain tumors was carried out by Moore in 1948 (1). Fluorescein was labeled with radioiodine and detected with a hand-held G-M counter. During the past 20 years technological developments have led to the use of $^{99m}$Tc and automatic scanners and cameras. But as yet, the reasons for the localization of the radioactive compound in the lesion have not been found (2–5).

This paper shows that vascularity of the neoplasm is correlated with positive brain scans in the series studied and probably is a factor in the unusual permeability of the disrupted blood-brain barrier.

MATERIALS

Records of patients who had brain scans at the Nuclear Medicine Unit of The University of Michigan were analyzed. Tissue sections were available for review in 107 cases and these formed the basis of the study. All the tissues were accessioned at the University of Michigan Department of Pathology from 1964 to 1967 and were obtained by craniotomy following brain scanning except for one autopsy case.

METHODS

Scan reading. The brain scans were done with four commercially available scanners (Picker Magna-scanners III and V and Ohio-Nuclear Models 54H and 54F). The agent used was $^{197}$Hg-chlormerodrin in a dose of 15 $\mu$Ci/kg (to a maximum of 1,050 $\mu$Ci) or $^{99m}$Tc-pertechnetate in a standard dose of 10 mCi. The brain scans were put into three groups, positive, negative and equivocal, using the initially reported clinical reading.

Histopathologic grading for vascularity. Routine sections cut 4–6 microns thick and stained with hematoxylin and eosin were used. Degree of vascularity was judged according to the size and number of patent arterial and venous channels present in the most vascular area of the lesion without knowledge of the brain-scan readings. The degree of vascularity was then compared to that of surrounding tissue whenever normal brain or meninges were included in the surgical specimen. If only the lesion was available, its vascularity was compared to that of routine necropsy sections of a similar area. The following grading system was used:

1+ less vascular than normal brain
2+ vascularity similar to that of normal brain
3+ definitely more vascular than normal brain
4+ highly vascular
5+ extremely vascular

All lesions were examined on two different occasions to try to ensure consistent evaluations. The same microscope was used throughout to maintain an unvarying field size and to keep the magnification constant.

Received July 5, 1968; revision accepted Feb. 28, 1969.

For reprints contact: Manfred H. Soiderer, Dept. of Pathology, Univ. of Michigan Medical Center, Ann Arbor, Mich. 48104.

* Present address: Nuclear Medicine Division, Mary's Help Hospital, Daly City, California 94015.

---

**FIG. 1.** Plot of data in $3 \times 5$ table according to brain-scan reading and tissue vascularity reading. Each small black dot represents one case. Small circles represent cases with vascular malformations, which as a group seem to be apart from main distribution. Inspection of raw data suggests a positive correlation. Using heavy lines, data were condensed into $2 \times 2$ table with four groups. Chi-square value was 13.6 with $p < 0.01$. It may be inferred from this figure that there is significant positive correlation between tissue vascularity and visualization on brain scan.
**FIG. 2.** L.R. #1067013. Anterior and right lateral positive brain scans and histopathological section of associated highly vascular meningioma (× 170). Scan was done 1 hr after injection of 10 mCi $^{131}$I with Ohio-Nuclear scanner with 5-in. crystal.

**Statistical analysis.** The original $3 \times 5$ table was condensed into a $2 \times 2$ table to eliminate cells with only a few members and to increase statistical validity. The scan reading headings used were “abnormal” and “not abnormal.” The equivocal and negative scans were placed together in the “not abnormal” group. The tissue vascularity readings used were “above normal” and “normal and below.” The standard chi-square analysis was done (Fig. 1).

**RESULTS**

Figure 1 shows the correlation of scan reading with tissue vascularity. The brain scans were from...
107 patients of whom 74 were read as positive, 18 were read as equivocal and 15 were read as negative. The tissue readings classified five as extremely vascular, 28 as highly vascular, 47 as definitely more vascular than normal brain, 21 as vascularity similar to that of normal brain and six as less vascular than normal brain. The great majority of positive brain scans were associated with above normal vascularity, and conversely, the majority of negative brain scans was seen in lesions of normal vascularity.

The chi-square value was 13.6, which indicates that this distribution would occur less than 0.01 of the time due to chance alone. It may be inferred from this figure that there is a significant correlation between tissue vascularity and positive brain-scan visualization. Figure 2 shows a positive brain scan and a histopathologic section of the associated meningioma which was graded 4+, as highly vascular. Figure 3 shows a negative brain scan and a section of the associated Grade II astrocytoma which had normal vascularity and was graded as 2+. 

FIG. 3. H.J. #287035. Anterior and right lateral negative brain scans and histopathological section of associated Grade II astrocytoma with normal vascularity (× 170). Scan was done 2 hr after injection of 10 mCi 99mTc with 5-in. Picker Nuclear scanner.
Visualization of an abnormal region in the brain with a radioactive substance depends on many factors including relative intensity of uptake, size, homogeneity of uptake, sharpness of borders, depth in the brain, proximity to normal structures with high uptake, time of observation, dose and gamma-ray energy of the radionuclide and the imaging devices and aids used by the physician (2).

Of these factors, little is known about the specific determinants of increased uptake in pathological brain tissue which make it possible to detect lesions in the midst of normal brain (3-5).

Since 1885 when Ehrlich (6) reported that normal brain would exclude certain substances in the blood, the blood-brain barrier has been the subject of much investigation and speculation. It has been assumed that alteration of the normal blood-brain barrier is the reason for the differential uptake.

The “barrier” is relative and the different concentrations seem to be a result of differential rates of absorption and excretion. Davson has reviewed the literature in a recent monograph (7).

Although some studies have suggested varying uptake with different agents (4,8-10), the similar clinical results have led most investigators to believe that the penetration and retention in pathologic lesions is due to nonspecific physical diffusion through an altered blood-brain barrier rather than selective concentration (11-17).

The varying uptake of vascular lesions with time has shed some light on the subject. Immediately after cerebral thrombosis the brain scan will usually be negative, become positive after 1 or 2 weeks and then frequently become negative a few weeks later. The time when the scan is positive coincides with the growth of new capillaries into the area of the infarct. These new, immature vessels could be expected to have an undeveloped blood-brain barrier which would be in line with current knowledge that this barrier is not well established until late in the development of the fetal brain. The time the scan reverts to normal coincides with the maturation of these vessels and development of a normal blood-brain barrier.

That the number of vessels is not the only determinant is shown by the frequently low brain-scan activity of hemangiomas which are composed of old mature vessels. Vascular tumors, however, contain relatively little tissue for uptake and are best seen when scanned shortly after injection of the agent while the blood levels are relatively high.

Alteration of the normal blood-brain barrier is assumed to be responsible for visualization of intracranial lesions on the brain scan. The specific factors are not known. To evaluate the importance of tissue vascularity as a factor, 107 brain scans with histopathological verification were studied. The tissue vascularity was then compared with the clinical brain-scan readings. Chi-square analysis of these data was interpreted as indicating a correlation of the degree of vascularity of the lesions with visualization on brain scan.

Of the five blood vessel tumors and vascular malformations, however, two were equivocal on brain scan and three were not visualized at all. This suggests that in addition to the degree of vascularity the maturity of the vessels and the relative metabolic activity of the tissue are factors in visualization although the visualization of these lesions may be by a different mechanism.

ACKNOWLEDGMENT

We wish to thank W. H. Beierwaltes, Director of the Nuclear Medicine Unit at The University of Michigan, for permission to use the scans and data which formed the basis of this study and to John A. Jacquez of the Department of Biostatistics for reviewing the statistical analysis. This work was supported in part by USPHS Training Grant 5 TICA-5134-04.

REFERENCES


Available Now

PROCEEDINGS OF THE SYMPOSIUM ON COMPUTERS AND SCANNING

Edited by John U. Hidalgo

The Proceedings of the "Symposium on Computers and Scanning," held at Tulane University on December 16–17, 1965, are now available from the Society of Nuclear Medicine at a cost of $5 ($5.50 outside USA). The symposium, which brought together speakers experienced in both the technology of computers and the technology of scanning, covered the many uses to which computers are now being put in nuclear medicine. The Proceedings contain 19 papers totaling 216 pages. Send orders to: The Society of Nuclear Medicine, 211 East 43rd St., New York, New York 10017.
Tissue Vascularity in Positive and Negative Brain Scans

Howard J. Cohn and Manfred H. Soiderer


This article and updated information are available at: [http://jnm.snmjournals.org/content/10/8/553](http://jnm.snmjournals.org/content/10/8/553)

Information about reproducing figures, tables, or other portions of this article can be found online at: [http://jnm.snmjournals.org/site/misc/permission.xhtml](http://jnm.snmjournals.org/site/misc/permission.xhtml)

Information about subscriptions to JNM can be found at: [http://jnm.snmjournals.org/site/subscriptions/online.xhtml](http://jnm.snmjournals.org/site/subscriptions/online.xhtml)