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These studies were supported by Contract #DE-AM03-76-SF00012 between the U.S. Department of Energy and the University of California

Prepared for the U.S. Department of Energy under Contract #DE-AC03-76-SF00012

THE RELATIONSHIP OF BRAIN IMAGING WITH RADIONUCLIDES AND WITH X-RAY COMPUTED TOMOGRAPHY

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UCLA - 12 - 1290

3 March 1981

THE RELATIONSHIP OF BRAIN IMAGING WITH RADIONUCLIDES AND WITH X-RAY COMPUTED TOMOGRAPHY

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SUMMARY:

1. Because of high sensitivity and specificity for altered local cerebral structure, x-ray computed tomography (CT) is the preferred initial diagnostic imaging study under most circumstances when cerebral disease is suspected. CT has no competitor for detecting fresh intracerebral hemorrhage.

2. Radionuclide imaging (RN) scan is preferred when relative perfusion is to be assessed, in patients allergic to contrast media, and when an adequate CT study is not technically possible.

3. (RN) plays an important complementary role to CT, especially for patients suspected of subacute or chronic subdural hematoma, cerebral infarction, arteriovenous malformations, meningitis, encephalitis, normal pressure hydrocephalus, or when CT findings are inconclusive.

4. When CT is not available, RN serves as a good screening study for suspected cerebral tumor, infection, recent infarction, arteriovenous malformation, and chronic subdural hematoma.

5. Future improvement in radionuclide imaging by means of emission computed tomography (ECT) is expected to provide details of local cerebral function which should be important diagnostic information, especially in situations unassociated with those local structural alterations required for diagnosis by CT.

METHODS

Radionuclide Imaging (RN)

Radionuclide imaging (RN) is defined here as a series of nontomographic pictures made by scintillation camera after intravenous or intrathecal injection of a radioactive indicator, i.e. radiopharmaceutical (1). Most commonly, the study is performed in two stages, as follows. First, a bolus injection of ^{99m}Tc-pertechnetate is injected intravenously and the scintillation camera records the passage of radioactivity ("flow study") through neck vessels and brain. Several hours later, brain radioactivity ("static study") is recorded in anterior, posterior, lateral and vertex views. The early flow study is a test of the patency of neck vessels and an estimate of regional perfusion in the brain. The later static study detects alterations in regional blood brain barrier permeability and regional increased blood volume. The flow study has good sensitivity for detecting asymmetry of carotid artery patency and regional cerebral blood flow in patients after stroke, and the static images have good sensitivity for detection of metastatic and primary brain tumors, subacute ischemic cerebral infarcts, local infection, arteriovenous malformations, and other lesions which damage the blood brain barrier. The RN study does not detect fresh hemorrhage, edema, calcifications, ventricular size or displacements, or cerebral atrophy. RN is widely available; scintillation cameras are common medical equipment, since these instruments are used for a variety of efficacious examinations in addition to examination of the brain. RN imaging is less affected by patient movement or the presence of intracranial metal than is the CT study. While there is a finite risk of allergic response to the intraveous injection of iodinated contrast media in CT, with pertechnetate RN there is none. Some authors have recommended ^{99m}Tc-DTPA and ^{99m}Tc glucoheptonate as preferred alternatives to ^{99m}Tc pertechnetate for routine brain imaging (2,3).

In radionuclide cisternography, or cerebral spinal fluid imaging, the changing pattern of distribution and absorption of CSF is imaged by scintillation camera after subarachnoid injection of indicators such as ^{111}In-DTPA. Usually images are made at 6 hours, 24 hours, and 48 hours after injection in order to image possible altered migration of radioactive CSF through intracisternal and supraconvexity pathways or, abnormally, its accumulation and retention within dilated ventricles.

Radionuclide imaging of ^{99m}Tc-diphosphonate is sometimes employed because of the preferred concentration of this agent in cerebral infarcts as compared to intracerebral tumors (56). Another adjunctive study is the imaging of ^{67}Ga-citrate, an agent with a preferred concentration in neoplasm rather than infarction (55) and sometimes helpful in the detection of recurrent tumor in follow-up examinations after surgery. Unless otherwise noted, in this paper the RN study refers to the routine scintillation camera imaging procedure with ^{99m}Tc-pertechnetate.

X-ray Computed Tomography (CT)

X-ray computed tomography (CT) is a reconstruction of x-ray transmission data which forms a nearly exact image of attenuation coefficients or tissue densities of an isolated section of the head (4,5). Without injection of contrast media, CT demonstrates with high sensitivity and specificity local mass lesions, hemorrhage, edema, and calcifications as well as ventricular size and displacements and cerebral atrophy. After intravenous injection of iodinated contrast media, CT also permits the detection of another class of lesions by means of extravascular accumulation of the indicator at sites of blood brain barrier alterations.

Together, RN and CT can give complementary data. RN alone detects altered blood flow; CT alone detects fresh hemorrhage and local structural alterations due to density change or displacement. Usually, both the static RN and the enhanced CT detect disruptions of blood brain barrier, but sometimes one study is normal while the other is abnormal.

Problems with Comparisons:

Numerous groups have now reported experience with CT and RN applied to a wide variety of cerebral disorders (6-23). Experimental design was commonly flawed by failures to meet the following requirements for avoiding bias (21,23).

1. Both examinations should represent optimal state-of-the-art method. For the RN scan, a modern, high-resolution, scintillation camera should be employed, a flow study should be performed, the static views should be obtained no sooner than two or three hours after injection, and a vertex view should be included. The CT scanner should be a rapid, modern instrument. Whether or not contrast enhancement was employed should be clearly recorded, along with how the decision was made. If multiple centers contribute images, secondary reviewers should not use a variable display format for RN if a uniform one is used for CT (21).
2. Methods of patient selection should be stated clearly. This is especially true for the study performed second in sequence. (e.g.: If the second study is performed only when the first is positive, results will be biased in favor of the first st[illegible]. If the second study is only performed when the first study is equ[illegible]ocal, results will be biased in favor of the second study.)
3. The interval in time between RN and CT should be brief; each should examine the same cerebral conditions. This is especially true in

stroke and in infection, where conditions and results depend strongly on when either study is performed.

4. In comparing examination results, a distinction should be made between information relevant to patient management and not.

In spite of difficulties in clinical experimental design, important information has come from these studies and from now extensive clinical experience. This is the basis for the following conclusions concerning application patterns of CT and RN.

PATTERNS OF APPLICATION

Neoplasms:

The sensitivity (approximately 80-85%) and specificity of RN for detection of intracranial neoplasms is very good; the sensitivity (approximately 95%) of CT is somewhat better and anatomic localization is considerably better.

With RN, diagnosis depends almost entirely on the static imaging of the blood brain barrier alteration. Sensitivity (54) depends on tumor histology, size, and location; low grade astrocytomas, 60-70%; malignant astrocytomas, greater than 90%; oligodendrogliomas, 80%; posterior fossa tumors, 80%; meningiomas, greater than 90%. The RN flow study will demonstrate hyperperfusion in approximately 75% of meningiomas. Sensitivities reported for mestastases are more variable, but probably are approximately 80%. RN is considerably less sensitive for pituitary, parasellar, and brain stem tumors which are only detected when very large.

With CT, detection can result not only from altered blood brain barrier shown in the contrast enhanced scan, but also on demonstration of ventricular enlargement and displacement, altered tumor attenuation, local edema, or calcification. Because of this, CT is considerably more sensitive in detecting of low grade gliomas, cystic lesions, and tumors of the base of the brain, such as pituitary and parasellar lesions. In addition, CT image features help distinguish primary from metastatic tumors, intracerebral from extracerebral tumors, and low grade from high grade gliomas (68).

When used together as complementary examinations, CT plus RN detect almost 100% of intracerebral neoplasms which cause symptoms and are later confirmed.

Both RN and CT are useful in follow-up examination after surgery, but CT is preferred because of its tomographic ability to avoid overlying artifact which can obscure RN findings. If CT is not available and the pertechnetate RN is confusing, an RN scan using ^{68}Ga-citrate can be useful for determining reappearance of tumor.

When CT is not available, RN remains an accurate initial imaging examination for patients suspected of intracranial neoplasms. When CT is available, it is the preferred examination of patients with focal presentations or generalized seizures of recent onset where intracranial neoplasm is suspected. If the patient has no sensitivitiy to contrast media, CT should be performed with contrast enhancement. If CT results do not agree with the clinical presentation, or if patient sensitivity precludes an enhanced CT scan, RN should be performed.

<u>Occlusive Cerebrovascular Disease:</u>

The usefulness of CT or RN in stroke depends much on the clinical situation and the timing of examination. The RN scan is preferred for perfusion estimates. Only CT can detect or exclude hemorrhagic infarction when anticoagulation is considered. The RN flow study detects severe stenosis of the common or internal carotid arteries and asymmetries of hemispheric cerebral blood flow. Unlike CT, the RN flow study permits an uncomplicated estimate of regional perfusion deficits or hyperemmia at any time after stroke. For a finite period, the RN static study will identify the infarct site as a region of altered blood brain barrier, primarily due to the development of neovascularity soon after stroke. Usually the static scan is normal during the first few days, the abnormality becomes maximum at 2-3 weeks, persists for many weeks, and then disappears. This same blood brain barrier alteration can also be seen in the enhanced CT scan, probably with similar sensitivity. On the other hand, the unenhanced CT early after stroke will show the presence of intracerebral, intraventricular, or subarachnoid hemorrhage, local reduced attenuation due to early edema, and later, the distribution of permanent tissue damage. Between the first week and the first month after stroke, either the enhanced CT or the static RN aid in distinguishing an infarct from a tumor, or a new infarct from an old one. When available, CT is preferred for this purpose because of superior anatomic definition.

Both the RN flow study and the enhanced CT can be extremely helpful in detecting the intracerebral arterial venous malformation and thrombosis of the superior saggittal sinus (24).

Head Injury:

The study of acute cerebral trauma is dominated by CT which is capable of revealing several types of lesions; hemorrhagic contusions, intracerebral and extracerebral hematomas, general and focal cerebral swelling, and shearing injury of the cerebral white matter (25). Early after trauma, the role of RN is limited; the RN flow study is capable of diagnosing the acute subdural hematoma with good sensitivity by demonstrating medial displacement of cerebral vasculature. By the end of the first week, the static RN scan will detect intracerebral hematoma and subdural hematoma because of blood brain barrier alterations, probably due to the formation of neovasculature adjacent to the hematoma site. In this early period after head injury, however, CT clearly demonstrates intracerebral hemorrhage as a dense image and the examination has no competitor.

Later the static RN scan gains in value. At times estimated from 7 to 90 days after injury, a subdural hematoma becomes isodense on the CT scan and diagnosis must depend on displacement alone. With this same passage of time, however, the static RN scan becomes increasingly positive. When isodense lesions are most likely to be present on CT, the RN scan has its highest sensitivity (91%) for chronic subdural hematomas (26). The RN scan is particularly useful when the isodense chronic subdural hematoma is bilateral and displacement effects are not obvious in CT scans (27).

Infection:

RN and CT detect cerebral absesses and other pyogenic inflamatory lesions with similar sensitivities, but CT distinguishes better cerebritis and focal abscess, and thus can be more useful for guiding therapy.

With more extensive and poorly organized inflammatory lesions of viral origin, there is disagreement as to whether RN or CT is more sensitive for early diagnosis (15,28,29). CT can show an early lesion of decreased attenuation, possibly related to early edema. RN is probably more sensitive than the enhanced CT for demonstrating early alterations in blood brain barrier because of the greater time allowed for tracer accumulation (3 hours) before imaging is performed. Early diagnosis is especially important in herpes simplex encephalitis. Localization to the site of predilection in the temporal lobe, when combined with appropriate clinical findings, suggests the diagnosis, guides brain biopsy, and permits early initiation of medical therapy, minimizing irreversible brain damage. Further investigation is required to settle this issue.

Dementia:

CT defines well the size and shape of the cerebral spinal fluid spaces and is usually the initial diagnostic imaging study performed in patients with dementia. RN cisternography plays a complimentary role in the evaluation of the demented patient suspected of having shunt-responsive normal pressure hydrocephalus (NPH). The diagnosis of obstructive communicating hydrocephalus is first inferred from CT; the degree of obstruction is estimated by the degree of ventricular reflux and stasis of the radiopharmaceutical on RN cisternography (30). This information is used as a guide to determine whether or not diversionary shunting is likely to relieve the patients symptoms, but diagnostic criteria for shunt-responsive NPH remain imprecise and controversial (31). CT cisternography has also been employed using metrizamide as a contrast indicator (32) for the same kind of information concerning CSF dynamics. At present, RN cisternography is preferred because it is more innocuous.

Further study is required to evaluate the relative merits of RN cisternography and CT-metrizamide cisternography for localization of CSF leaks through dural fistulae. CT has the potential for more precise localization. RN is preferred for evaluating the functioning of CSF diversionary shunts; the method is simple and fine anatomic detail is usually not required.

FUTURE DIRECTIONS

Imaging Local Brain Function:

In the examples discussed here, the RN flow study is preferred for questions relating to relative regional blood flow and cerebrospinal fluid dynamics; CT is preferred for the more common questions concerning local structural alterations in the brain. In addition to blood flow, other physiological correlates of altered cerebral function are expected to become increasingly important in medical management as the capabilities of non-invasive study methods are extended. Although CT demonstrations of physiological features such as cerebral blood flow and cerebral blood volume are now possible as research efforts (64-67) functional data are more naturally available by extension of RN, where a potentially vast choice of natural or artificial radioactive indicators is possible and the mass of material injected into the patient is extremely small.

For example, the radioactive xenon blood flow study can be used for quantitative and absolute measurements of regional cerebral blood flow. The radioactive gas ^{133}Xe is delivered by intravenous or inhalation route and counted by detectors placed against the head (33, 34). This method is potentially available for community hospital use, but has been employed considerably less frequently in routine clinical practice than has the RN flow study. It is a valuable tool for studying the pathophysiology of the cerebral circulation, especially in stroke, head injury, and epilepsy. More sophisticated estimates of regional perfusion and oxygen extraction have been accomplished using cyclotron-produced radionuclides such as ^{15}O (35). These studies are now limited to research centers, but are important steps in advancing knowledge of cerebral pathophysiology.

However, for real improvement in the study method, new RN techniques should provide local rather than regional data on altered cerebral functions. It is now understood that important alterations in small parts of the brain can be obscured when averaged over larger regions or hemispheres.

The most promising approach to this is the rapidly evolving technique of emission computed tomography (ECT), which should benefit from the potentially wide variety of indicators possible with the RN method, as well as the same accurate cross-section display available in CT. ECT is a non-invasive scanning method which produces a cross-section picture of brain radioactivity following intravenous injection of a radioactive indicator. ECT (36, 37) and CT (38-40) have developed independently, but the reconstruction processes are conceptually identical (4, 5).

The ECT method may be characterized further according to the kind of radionuclide used. In single-photon ECT (SPECT), ordinary radionuclides such as ^{99m}Tc are used (41,60); with positron ECT (PECT), positron-emitters are used which require production in an on-site cyclotron (42,43). SPECT is more applicable for widespread use, but biologically important indicators are limited now. PECT is the more important research method now, since many significant substrates and tracers can only be labeled with cyclotron-produced ^{18}F, ^{11}C, ^{13}N, and ^{15}O. More widespread use of SPECT depends on radiopharmaceutical innovation (61-63), of PECT on the development of less expensive accelerators and scanners. Although SPECT of ^{99m}Tc pertechnetate has been shown to be more sensitive and specific than RN for detecting alterations in the blood brain barrier (44-46), the more important contributions of both SPECT and PECT are expected to be in the demonstration of local cerebral metabolic and circulatory physiology previously restricted to animal models of disease (41, 47-53). For example, the cerebral images of glucose utilization produced by PECT of ^{18}F-fluorodeoxyglucose (49,57,58) help identify dysfunctional brain zones which are negative to CT but responsible for seizures (51) and post-stroke aphasia (50,59).

With further development, the ECT radionuclide method should be useful in improving understanding of how the human brain responds to disease states, and may help in diagnosing and categorizing better those various cerebral disorders in which changes of brain function are not associated with perceptable changes in brain structure.

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