CRANIAL SCINTIPHOTOGRAPHIC BLOOD FLOW DEFECTS IN ARTERIOGRAPHICALLY PROVEN CEREBRAL VASCULAR DISEASE

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The accuracy and sensitivity of rapid sequential cranial scintiphotography after intravenous bolus injection of ^{99m}Tc in CVD were assessed by correlation with the vascular changes and clinical phases of 84 angiographically proven cases of CVD. Patients were divided into three clinical groups: (A) asymptomatic and transient ischemic attacks; (B) acute and subacute strokes; (C) chronic completed strokes. Abnormality of the scintiphotographic study was noted in 53% of Group 1, 83% of Group 2, and 75% of Group 3. Of those with isotopic abnormalities, all except one patient had a BF abnormality. Most patients in Group 1 were without BBB defects, and only half of the patients in Group 2 and one-third of the patients in Group 3 with BF abnormalities had BBB defects. Correlation of BF studies with specific arteriographic findings revealed isotopic abnormalities in 68% of the patients with extracranial vascular disease and 85% of patients with intracranial vascular disease. While less frequent, BBB defects occurred in 25% of the patients with extracranial involvement and in 44% of patients with intracranial involvement. These studies also indicate that the frequency of BF abnormalities correlated with the severity of vascular involvement and the degree of symptomatology.

The overall diagnostic accuracy in this study of 75% is noteworthy because over one-half of the patients were not in the acute or subacute phase of their disease. Use of conventional BBB studies alone would reduce overall diagnostic accuracy from 75 to 32%.

Conventional radionuclide imaging of focal intracranial processes is dependent upon localized increases of administered activity as a result of focal alterations of the blood-brain barrier (BBB). In patients with cerebral vascular disease (CVD), such BBB defects occur as a result of acute infarction (*1–8*). However, the vast majority of patients with CVD are without acute infarction at any given time. This large and most important segment of patients may already have significant alterations in cerebral circulation and does not manifest abnormalities by conventional static scintiphotography. This includes those patients without cerebral symptoms, with transient symptoms, with chronic and progressive symptoms, and patients seen immediately after the acute onset of a neurologic deficit. Static radionuclide images are generally entirely normal in these patients.

Rapid sequential cranial scintiphotography after intravenous bolus injection of a high-flux, short-lived nuclide such as ^{99m}Tc has allowed for the imaging of cranial vascular filling and regional perfusion (*9–11*). This procedure affords a safe and practical means of detecting the various phases of CVD.

In the present study, the accuracy and sensitivity of this dynamic radioisotopic approach were assessed by correlation with clinical status and arteriographic determination of sites and degrees of stenosis and occlusion in patients with CVD.

MATERIALS AND METHODS

This study involved all patients with arteriographically proven CVD who had undergone both cerebral angiography and rapid sequential cranial scintiphotography during the three-year period from December 1966 to December 1969 at the San Francisco General Hospital. Since December 1966, all cranial radioisotope imaging studies performed by the nu-

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clear medicine laboratory have routinely included rapid sequential imaging after bolus injection. During the period of this study, 1,836 such procedures were performed. The 84 patients involved in the present study were not preselected. They were clinically investigated either because of diagnostic problems or for evaluation of extracranial vascular surgery. Consequently, there was a relatively small number of obvious acute stroke patients. In almost all cases, isotope encephalography and cerebral angiography were performed within one to two weeks of each other. On the bases of history, physical findings, and course, the patients were divided into three clinical groups: (A) no neurologic symptoms (all patients had other evidence of vascular disease, e.g., neck bruit, claudication, etc.) and transient ischemic attack (TIA) (history of neurologic symptoms lasting less than 24 hr with no residual focal sign); (B) acute and subacute cerebrovascular accident (persisting focal neurologic symptoms and signs with onset up to six weeks before study; and (C) chronic cerebrovascular accident (focal neurologic symptoms and signs with onset longer than six weeks before study).

Cerebral angiography was performed in almost all cases by use of a retrograde femoral artery catheter. Almost all patients had bilateral carotid artery studies and, when indicated, they also had vertebral basilar angiography. Vascular disease was classified as being predominantly intracranial or extracranial, with either bilateral or unilateral involvement. Extracranial lesions were further subdivided into: (A) greater than 80% occluded and (B) less than 80% occluded.

Cranial vascular filling and the presence of a BBB was evaluated by rapid sequential cranial scintiphotography and 1-hr static imaging. These studies were performed by previously described methods, using an Anger scintillation camera and ^{99m}Tc-pertechnetate (*10*). This method involves: (A) an antecubital intravenous bolus injection of 10–15 mCi of ^{99m}Tc-pertechnetate; (B) a rapid sequence of (anterior or anterior Towne's view) 1.5-sec scintiphotos obtained immediately after bolus injection; and (C) standard, delayed, 1-hr multiview cranial scintiphotos for the detection of BBB defects.

The series of rapid sequential cranial scintiphotos were examined without previous knowledge of angiographic findings for asymmetries of timing and degree of cranial filling by the isotope bolus as it passed through the vascular structures of the cerebral hemispheres. Special attention was given to the relatively early phases of cranial arterial filling and capillary perfusion. The static scintiphotos taken at 1 hr were evaluated for the presence or absence of BBB defects.

TABLE 1. PATIENT GROUPINGS ARTERIOGRAPHICALLY PROVEN CEREBRAL VASCULAR DISEASE

Clinical		Angiographic	
Asymptomatic/TIA	19	Intracranial	32
Acute/subacute	41	Extracranial	52
Chronic	24		
Total	84	Total	84

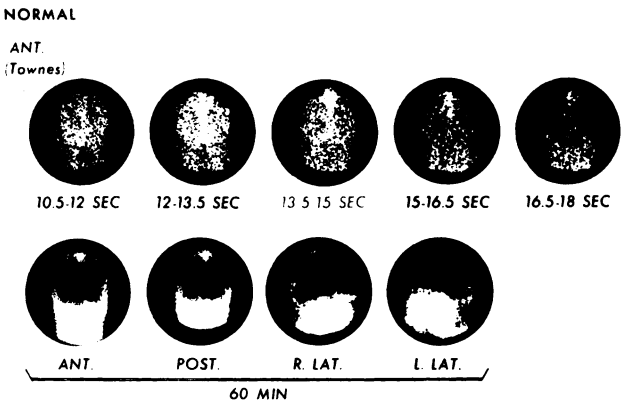

FIG. 1. Anterior Towne's view rapid sequential and 1-hr multiview cranial scintiphotographic study in normal patient.

RESULTS

The distribution of the 84 patients with arteriographically proven CVD is shown in Table 1 by clinical phase of disease and according to arteriographic findings. Although the number of patients in each group is not equal, a significant number of cases is present in each category.

For reference and comparison, an anterior Towne's view rapid sequential and a 1-hr multiview cranial scintiphotographic study in a normal subject are shown in Fig. 1. The scintiphoto taken at 10.5–12.0 sec after injection shows filling of the major neck arteries and their confluence at the circle of Willis, the midline region of the anterior cerebral distribution, and the bilateral regions of distribution of the middle cerebral arteries. At 12.0–13.5 sec, the filling of the cerebral areas as described above has increased, associated with a diffuse distribution of capillary activity throughout the cerebral hemispheres. At 13.5–15.0 sec, the venous phase of this cerebral vascular transit of ^{99m}Tc is noted by the prominent filling of the superior sagittal sinus. The remainder of this rapid sequence of scintiphotos shows a progressive decrease in cranial activity as the radionuclide bolus passes through and exits from the vasculature of the head.

An example of scintiphotographic changes throughout the course of a typical stroke patient is shown in Fig. 2. The patient was a 49-year-old woman who

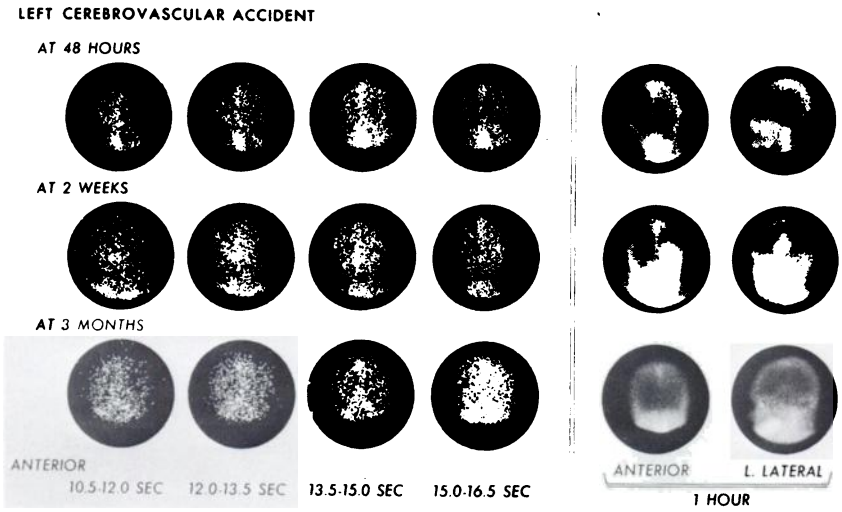

FIG. 2. Scintiphotographic changes at 48 hr, 2 weeks, and 3 months, following left cerebrovascular accident.

presented with the acute onset of a right hemiplegia and aphasia because of a left cerebral vascular occlusion. The initial study that was performed 48 hr after the onset of symptoms is shown in Fig. 2. At 9.0–10.5 sec, decreased and delayed vascular filling is noted in the left middle cerebral vascular region.

The left cerebral hemisphere eventually shows a delayed vascular filling phase in the 12.0–13.5-sec, 13.5–15.0-sec, and 15.0–16.5-sec scintiphotos, at which time the radionuclide bolus is leaving the right cerebral vascular distribution. No focal BBB defect is noted in the 1-hr multiview studies. When studied at two weeks after the onset of symptoms, the development of a prominent left temporal parietal BBB defect was noted. Finally, the patient was re-studied at three months after the onset during the chronic phase of her disease when she exhibited only a very mild weakness of the right arm. At that time, the rapid sequential study showed persistence of the decreased and delayed left cerebral vascular filling pattern similar to the initial study. The 1-hr study showed a very slight residual accumulation of activity in the left temporal parietal region.

An example of rapid cranial scintiphotographic changes in a patient with TIA is shown in Fig. 3. The patient, who is a 56-year-old man with a previous history of TIA, was studied 48 hr after experiencing a transient mild right hemiparesis and aphasia. Arteriography revealed occlusion of several small branches in the left-middle cerebral artery distribution. This study showed decreased and delayed vascular filling in the region of distribution of the left-middle cerebral artery. This abnormality, although noted in all scintiphotos, is best seen in the initial scintiphotos taken at 12.0–13.5 sec. The 1-hr studies showed no evidence of a BBB defect.

An example of altered cranial vascular filling in asymptomatic occlusive cerebral vascular disease is shown in Fig. 4. By arteriographic studies, this 82-year-old man was found to have complete occlusion of the right common carotid artery and good collateral filling from an enlarged anterior communi-

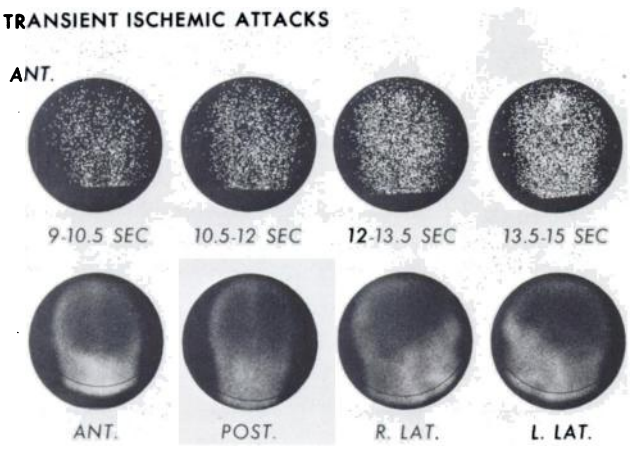

FIG. 3. Rapid cranial scintiphotographic changes in patient with TIA.

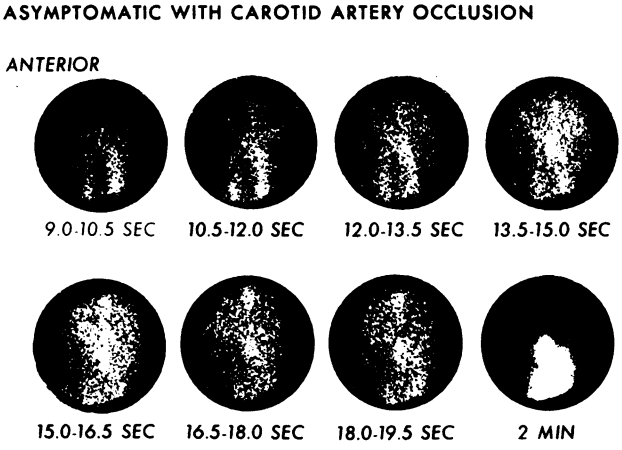

FIG. 4. Altered cranial vascular filling in asymptomatic right carotid artery occlusion.

TABLE 2. CORRELATION OF ^{99m}Tc BLOOD FLOW AND BLOOD-BRAIN BARRIER ABNORMALITIES WITH CLINICAL PHASES OF CVD

Clinical phases	No. of patients	No. of BF abn. only	No. of BF + BBB abn.	No. of BBB only	Total BF abn. No.	Total BF abn. %	Total BBB abn. No.	Total BBB abn. %
Asymptomatic/TIA	19	9	1	1	10	53	2	10
Acute/subacute	41	15	19	0	34	83	19	46
Chronic	24	12	6	0	18	75	6	25
All phases of CVD	84				62	74	27	32

cating artery. Decreased filling of the right carotid artery is noted beginning with the 9.0–10.5-sec scintiphoto. At 10.5–12.0 sec and 12.0–13.5 sec, a definite delay and decrease in blood flow in the right-middle cerebral distribution are noted. In the subsequent scintiphotos, the delayed collateral blood flow from the left carotid via the anterior communicating artery can be readily appreciated.

The correlation of results of the rapid sequential ^{99m}Tc blood flow (BF) and static BBB studies with the clinical phases of cerebrovascular disease is summarized in Table 2. Abnormalities in the BF phases of the study were noted in 53% of the Asymptomatic/TIA Group, in 83% of the Acute/Subacute Group, and in 75% of the Chronic Group. Most patients without neurologic symptoms or with TIA did not have BBB defects, and only approximately one-half (19/34) of the patients in the Acute/Subacute Group and one-third (6/18) of the patients in the Chronic Group with BF abnormalities had BBB defects. The enhancement of diagnostic sensitivity by use of the BF procedure over the conventional BBB procedure was greatest in the Asymptomatic/TIA Group (BF abn., 53%; BBB abn., 10%), with highly significant improvements in the Acute/Subacute Group (BF abn., 83%; BBB abn., 46%) and Chronic Group (BF abn., 75%; BBB abn., 25%). Relative to all phases of CVD, 74% exhibited BF abnormalities, whereas only 32% were associated with BBB alterations.

Correlation of the BF and BBB studies with the arteriographic findings is summarized in Tables 3 and 4. Patients were classified as primarily exhibiting extracranial angiographic abnormalities (Table 3) or intracranial angiographic abnormalities (Table 4). Both groups were subdivided as to unilateral or bilateral involvement, and the extracranial group was subdivided further as to the degree of carotid occlusion, <80% vs >80%. In the group with extracranial lesions (Table 3), 68% of the patients exhibited isotopic abnormalities. All patients except one had a BF abnormality. Approximately one-third of the patients exhibiting isotopic abnormalities in this group had a BBB defect. Although there was no

TABLE 3. CORRELATION OF ^{99m}Tc BLOOD FLOW AND BLOOD-BRAIN ABNORMALITIES WITH EXTRACRANIAL ARTERIOGRAPHIC CHANGES

	No.	BF abn. only	BF + BBB abn.	BBB abn. only	Total abnormals No.	Total abnormals %
Unilateral						
<80%	7	2	1	0	3	43
>80%	26	11	9	0	20	77
Bilateral						
<80%	13	6	0	1	7	54
>80%	6	3	2	0	5	83
Total	52	22	12	1	35	68

TABLE 4. CORRELATION OF ^{99m}Tc BLOOD FLOW AND BLOOD-BRAIN ABNORMALITIES WITH INTRACRANIAL ARTERIOGRAPHIC CHANGES

	No.	BF abn. only	BF + BBB abn.	BBB abn. only	Total abnormals No.	Total abnormals %
Unilateral	29	11	13	0	24	83
Bilateral	3	2	1	0	3	100
Total	32	13	14	0	27	85

significant difference as to the presence or absence of isotopic abnormalities between patients with unilateral involvement as compared with bilateral extracranial involvement, there was a higher probability of detecting an isotopic abnormality in the >80% occluded group as compared with the <80% occluded group ($p < 0.10$).

In cases with primarily intracranial cerebrovascular disease (Table 4), 85% of the patients exhibited isotope encephalographic abnormalities. Of these patients, all had BF abnormalities, whereas approximately one-half also had BBB defects. No significant differences as to the presence or absence of isotopic abnormalities were noted between unilateral as compared with bilateral involvement.

The overall incidence of isotopic abnormalities was somewhat similar in the extracranial and intracranial groups. It was also noted that the location

of the vascular lesion (intracranial as compared with extracranial) was not related to the detection of BF and BBB abnormalities in the Asymptomatic/TIA Group ($p = 0.57$) and the Chronic Group ($p = 0.60$). However, it was found that the probability of detecting isotopic abnormalities was significantly greater ($p = 0.07$) in acute and subacute patients with intracranial vascular disease.

DISCUSSION

The use of radionuclide imaging procedures for the detection of focal intracranial processes has been due to its relative ease, safety, and diagnostic sensitivity. With reference to cerebral vascular disease, the initial applications were concerned with the detection of focal alterations of the BBB due to cerebral infarction. The results of such studies (*1–8*) have been quite similar, showing minimal changes during the first week after onset of symptoms, with increasing frequency of abnormalities that become more intense during the second to fourth week, and a gradual return to normal over the ensuing two to three months. These studies were performed mostly in typical stroke patients with relatively recent and, for the most part, moderate-to-severe symptoms and findings. Depending upon the timing and repetition of these studies and the severity and extent of the cerebral pathology, focal BBB abnormalities were detected in 33–63% of cases. The detection of BBB defects in 46% of the Acute/Subacute Group (Table 2) of the present study is consistent with this previous experience. The lower frequency of BBB defects in the Asymptomatic/TIA Group (10%) and the Chronic Group (25%) is to be expected in these nonacute phases of CVD. A majority of patients with CVD is without acute or subacute infarction and therefore will not exhibit any BBB defects as detected by conventional static scintiphotography. Yet it is this very group of patients who must be identified to determine the true course of CVD and, hopefully, devise effective means of preventing strokes that result in irreversible brain damage. The diverse pathologic conditions causing CVD all ultimately affect cerebral blood flow. Therefore, the detection and serial monitoring of altered cranial vascular filling and cerebral perfusion afford the most direct and sensitive means of identifying and studying patients with CVD.

A noninvasive approach to the problem of detecting cranial blood flow abnormalities has been the rapid sequential cranial scintiphotography after an intravenous bolus injection of a nondiffusible, high-flux nuclide such as ^{99m}Tc (*9–11*). Especially with reference to CVD (*12–25*), this approach is gaining increasing acceptance because of its ability to detect and characterize intracranial lesions that are undetectable by conventional BBB brain imaging procedures, and because it can be performed easily, safely, and in conjunction with conventional static studies.

Even though an intravenous bolus injection of ^{99m}Tc is modified by its transit through the heart and lungs, a significant degree of diagnostic sensitivity can be obtained from the study of patients with CVD. The present study indicates that the routine use of the sequential scintiphotographic BF studies results in greater than a doubling (32% vs 74%) of the detection of meaningful abnormalities in the entire spectrum of patients with CVD. This increased detection of abnormalities by the combined use of BF and BBB studies has been noted by other investigators (*26*). Somewhat similar studies of rapid sequential cranial scintiphotography after i.v. ^{99m}Tc in patients with CVD showed BF abnormalities in 37–86% of cases (*27–29*), compared with our finding of 74% with abnormal BF studies. Differences in results undoubtedly are due to variations in degree and type of vascular obstructive lesions in each group as well as the variations in the technique and the interpretation from study to study. There was significant improvement in detection of abnormalities using the BF studies in the Acute/Subacute Group (46% vs 85%) and the Chronic Group (25% vs 75%), and an even greater degree of improvement (10% vs 53%) in the most important Asymptomatic/TIA Group.

Relative to the predominant site of vascular involvement, a somewhat greater incidence of BF abnormalities occurred in patients with intracranial CVD (85%) as compared with extracranial CVD (68%). This observation may relate to: (A) a greater degree of collateral circulation possible with proximal disease as compared with distal involvement and (B) increased severity of disease in those patients with intracranial vascular involvement. The latter hypothesis is consistent with the current concept that a significant number of strokes result from extracranial emboli to the intracranial system (*30,31*). The increased number of BBB defects (infarcts) noted in patients with intracranial vascular diseases (44%) as compared with those with extracranial involvement (25%) supports such a hypothesis.

In relation to the degree of severity of vascular occlusion as defined by arteriography, no significant difference in BF abnormalities was noted in the groups exhibiting predominantly intracranial (Table 4) and extracranial (Table 3) involvement. However, when examining the extracranial disease

group alone, a greater incidence of BF abnormalities was noted in those patients with greater than 80% occlusion of the carotid artery (78%) as compared with those with a lesser degree of occlusion (50%).

Despite this high incidence of BF abnormalities, a number of patients with arteriographically proven CVD do not exhibit any such radioencephalographic changes. This inability to detect patients with CVD may be due to either: (A) small size and/or transient nature of BF defect; (B) posterior and/or inferior location of an abnormality; (C) the presence of a well-developed collateral circulation; or (D) the lack of hemodynamically significant occlusive disease. Probably it is also due to technical limitations of the current procedure. From our own experience and that of other investigators (*26–32*), proper evaluation of the early cranial vascular filling (arterial) phase is most important in detecting patients with CVD. Because of bolus elongation and because of the transient nature of vascular filling asynchronies due to small size and/or collateral flow, sequential scintiphotos should be taken rapidly at 1–2-sec intervals. Longer integration of scintiphoto data tends to obscure significant early changes and thus decreases the sensitivity of the technique. The visual interpretation of the low and rapidly changing rate of radionuclide accumulation, noted especially in the early vascular filling phase, may be very subjective if the changes are not marked.

A quantitative approach using a computer data processing of camera output would eliminate a large "grey zone" of subjectivity inherent in the visual interpretation of photographic images (*22,26,33*). Using an intravenous bolus injection of ^{99m}Tc and the gamma camera coupled to a computer system, Janeway, et al (*22*), have begun to define quantitatively the degree of normal asymmetry of cerebral blood flow, comparing one hemisphere or hemispheric region to its respective contralateral area. It has been shown that such quantitative limits for interpretation are narrower than those possible by visual interpretation (*26*). It is apparent that such an objective approach would allow for quantitative comparisons when monitoring the patient's course and the possible effects of therapy.

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