Regional Cerebral Blood Flow Scintigraphy in Tick-Borne Encephalitis and Other Aseptic Meningoencephalitis

Göran Günther, Mats Haglund, Laszlo Mesko, Staffan Bremmer, Lars Lindquist, Marianne Forsgren, Birgit Sköldenberg and Ulf Rudberg

Divisions of Infectious Diseases, Medical Radiology and Hospital Physics, Danderyd Hospital; Departments of Infectious Diseases and Clinical Virology, Huddinge Hospital, Karolinska Institute Danderyd Hospital, and Huddinge Hospital, Stockholm, Sweden

In a prospective study, regional cerebral blood flow (rCBF) was studied in patients with aseptic meningoencephalitis at 6 wk and 1 yr after onset of disease. **Methods:** Patients with tick-borne encephalitis ([TBE] n = 73) and meningoencephalitis of other etiology ([non-TBE] n = 56) were investigated with rCBF-scintigraphy (SPECT). SPECT images in the acute phase of disease and at long-term follow-up were analyzed for blood-flow disturbances and their localization in the central nervous system and were correlated to clinical course and outcome. **Results:** Decreased rCBF was seen in 50% of patients after 6 wk (TBE 49%, non-TBE 50%) and in 46% (TBE 47%, non-TBE 46%) after 1 yr. The decrease in rCBF was moderate in 18% and 11% at 6 wk and in 8% and 9% at the 1-yr follow-up of TBE and non-TBE patients, respectively. Reduced rCBF was significantly more common among patients with encephalitis than among those with meningitis, and more common in males. The distribution of cerebral flow changes was predominantly patchy or multifocal. At long-term follow-up, improvement in rCBF was seen in 28 of 109 patients (26%), but worsening of decreased rCBF was demonstrated in 19 of 109 (17%). In TBE patients, remaining neurological symptoms at 6 wk of disease were associated with worsening of decreased rCBF at the 1-yr follow-up. **Conclusion:** With SPECT, rCBF changes, mostly slight and patchy or multifocal, were detected in patients with aseptic meningoencephalitis. Decreased rCBF was more frequent in patients with moderate-to-severe encephalitis, although the clinical use in predicting long-term outcomes in aseptic meningoencephalitis (e.g., TBE) seems limited.

Key Words: human; tick-borne encephalitis; viral meningoencephalitis; brain SPECT; technetium-99m-HMPAO

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Viral meningoencephalitis usually runs a benign course, but is influenced by etiology and individual factors. Tick-borne encephalitis (TBE) is caused by a flavivirus related to dengue-fever, Japanese encephalitis and yellow fever viruses. Two subtypes of TBE virus (TBEV) are identified, western and eastern (*1*). The TBEV western subtype is transmitted through bites by *Ixodes ricinus* and appears endemic in the Swedish eastern archipelago, the Baltic Sea area, Russia and parts of central Europe (*2*). The disease has been known in Scandinavia since the early 1940s. The annual reported incidence in Sweden during the past decade was between 40 and 116 cases (*3–5*). The seroprevalence in endemic areas is 4%–22% (*6*). TBEV constitutes a major human pathogenic agent among tick-borne flaviviruses, and many patients suffer protracted neurological and cognitive dysfunction (*4,7–9*).

Understanding of the pathogenic mechanisms in TBE is incomplete. In a few lethal human cases neuronal necrosis, inflammatory reaction involving blood vessels and spongiform focal necrosis of white and predominantly gray matter are described (*10–12*). SPECT is used to study the regional blood flow of the brain. This method is considered more sensitive than MRI in detecting functional central nervous system (CNS) disturbances (*13*) and has been used to diagnose Alzheimer's dementia and other neurological disorders (*14–18*). There are also flow studies of viral meningoencephalitis, mainly in pediatric patients (*19,20*), human immunodeficiency virus (HIV) (*21–23*) and herpes simplex virus (HSV) encephalitis (*24–27*), but none in TBE. The aim of this study was to disclose any changes in cerebral blood flow, both acute and at long-term follow-up and to find whether such flow changes could be related to the clinical course and outcome in patients with TBE. A further objective was to study whether the regional cerebral blood flow (rCBF) pattern was different in TBE than in aseptic meningoencephalitis of other etiology.

MATERIALS AND METHODS

After giving informed consent, 130 patients with clinical symptoms and signs of acute viral meningitis and cerebrospinal fluid (CSF) pleocytosis with or without encephalitis entered the study from 1991 to 1993. One hundred and nine patients were evaluable with SPECT after 1 yr. Severe dementia developed in one patient, who was excluded from the study, and 11 patients with TBE and 9 patients with non-TBE (HSV 2: n = 1, enterovirus: n = 3 and unknown etiology: n = 5) could not be examined after 1 yr. Two patients became pregnant, 1 moved abroad and 17 refused second examination.

Of the evaluable patients, 73 were included in the study, representing prospective TBE patients randomly selected from consecutive patients. The male-to-female ratio was 37:36, with a median age of 42 yr (range, 18–69). Aseptic meningoencephalitis was of non-TBE etiology in 56 patients, included prospectively as a reference group (non-TBE), with a male-to-female ratio of 23:33, a median age of 35 yr (range, 16–69). Established diagnoses were enteroviral infection in 24 patients (echo 30 n = 5, echo 5 n = 1, echo 6 n = 1, echo 11 n = 1, coxsackie A9 n = 4, coxsackie B5 n = 1 and not specified type n = 11), HSV 2 in 9 patients, and HSV 1 and cytomegalovirus infection in 1 patient each. In 21 patients the cause remained unknown.

The initial clinical presentation of meningoencephalitis was classified as mild, moderate or severe. In mild disease (TBE: n = 37, non-TBE: n = 48) the symptoms were predominantly meningeal (fever, headache, rigidity of the neck, nausea and vomiting). Moderate-to-severe disease (TBE: n = 36, non-TBE: n = 8) was defined as focal or multifocal encephalitic symptoms and/or more intense diffuse dysfunction of the CNS (altered consciousness, slow cerebration, ataxia, tremor and dysphasia) present at onset of

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For correspondence or reprints contact: Göran Günther, MD, Division of Infectious Diseases, Karolinska Institute Danderyd Hospital, S-182 88 Danderyd, Sweden.

the disease. Nine of 73 patients with TBE (12%) developed severe myelitis and/or radiculitis followed by paresis of the spinal nerves. At clinical follow-up after 6 wk and 1 yr, respectively, 53 of 62 (85%) and 28 of 62 (45%) TBE patients and 25 of 47 (53%) and 12 of 47 (26%) non-TBE patients had not recovered and had symptoms including decreased memory and/or concentration capacity, ataxia, tremor, dysphasia, spinal nerve and cranial nerve (n. VIII) paresis.

Viral Diagnosis

TBE was diagnosed by the demonstration of specific IgM activity [μ-capture IgM enzyme-linked immunoabsorbent assay (ELISA)] in serum, verified with a significant rise in complement-fixing activity between acute- and convalescent-phase sera (*28*).

Enteroviral infection was diagnosed by isolation of virus from CSF and/or fecal sample (*29*) or by demonstration of enteroviral ribonucleic acid by polymerase chain reaction (PCR) in CSF (*30,31*). Alternatively, infection was diagnosed by significant rise in, or high, IgG activity in combination with significant change in paired IgM titers (*32*) or significant rise in complement-fixing activity.

HSV 1 and 2 CNS infections were diagnosed by the demonstration of HSV deoxyribonucleic acid (DNA) in CSF by PCR and/or intrathecal production of anti-HSV activity by capture-ELISA in CSF and serum (*33,34*). HSV PCR-DNA analyses were performed in patients with negative TBE IgM analysis.

rCBF Scintigraphy

For 6-wk analyses SPECT was performed at a median of 45 days after onset of meningoencephalitis, with a range of 26–196 days. For 1-yr follow-ups, the median was 11 mo, with a range of 11–17 mo.

Radiopharmaceutical

Technetium-99m-hexamethyl propyleneamine oxime (HMPAO) was prepared from a freeze-dried kit according to the manufacturer's instructions (Ceretec®; Amersham Medical Ltd., London, UK). HMPAO is a highly soluble lipophilic macrocyclic amine with rapid brain uptake, but with only moderate first-pass extraction. The pharmaceutical remains fixed in the brain after conversion to a hydrophilic compound in the presence of intracellular gluthatione (*35*). Once trapped in the gray matter, HMPAO is stable with little washin or washout effect over 6–8 hr. Ceretec® is thus a suitable ^{99m}Tc labeling kit for rCBF scintigraphy (*36,37*).

Patient Handling and Imaging Procedure

Each patient was placed comfortably supine on a bed in a quiet room with dimmed lights. A 1.2-mm (18-gauge) cannula (Venflon 2, Viggo BOC Ohmeda Ltd., Helsingborg, Sweden) was inserted into an antecubital vein. Ten to 15 minutes later the radiopharmaceutical was given as a bolus injection. Each patient remained silent, immobilized and with eyes closed for 2 min postinjection.

SPECT was performed with a conventional rotating gamma camera (GE 400 ACT; Milwaukee, WI) using a high-resolution collimator and an elliptical rotation orbit. Data were collected in 128 × 128 matrices using 64 angular increments over 360°, with an acquisition time of 30 sec/projection. Tomographic slices in transaxial, coronal and sagittal planes were reconstructed with a backprojection algorithm using a Hanning filter with a cutoff frequency of 0.9 cm^{-1} and attenuation correction. Data were reoriented to produce identical slices, parallel to the intraorbitomeatus line.

Image Analysis

Two experienced radiologists/nuclear medicine physicians visually assessed the rCBF images on the computer screen in consensus. This evaluation was blinded for clinical data and diagnosis. Transaxial, coronal and, when necessary, sagittal slices were used.

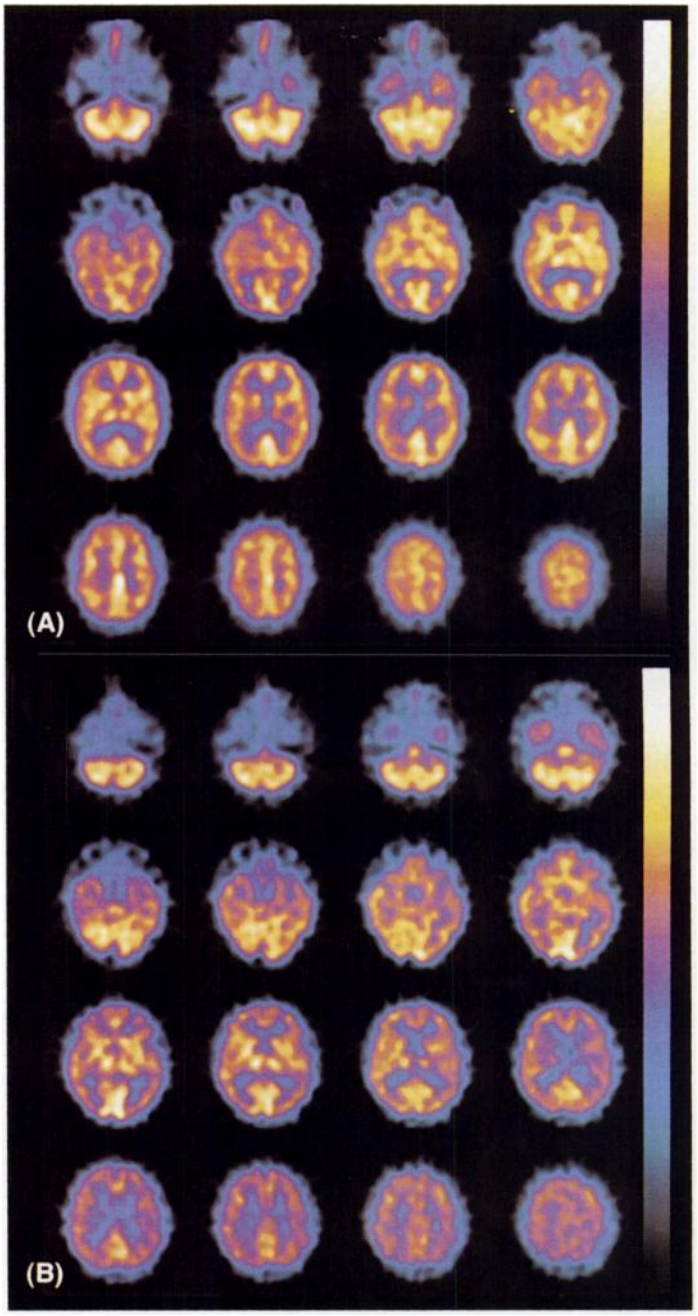

FIGURE 1. Transaxial slices (SPECT) in two patients with TBE. (A) Woman (32 yr) examined 44 days after onset of mild meningoencephalitis with paralysis of urinary bladder. Normal rCBF. (B) Man (60 yr), with dysesthesia, examined 43 days after onset of moderate encephalitis. Decreased rCBF (flow rate 2) with generally patchy pattern bilateral.

Transaxial and coronal examinations were displayed simultaneously. Reduction of rCBF was rated in eight separate regions in the brain: frontal left and right, frontoparietal left and right, parietal left and right and temporal left and right using a 4-grade scale, where 0 = no reduction, 1 = slight reduction, 2 = moderate reduction and 3 = severe reduction (*15*). The visual rating of the rCBF was done using the color scale as a reference (Figs. 1 and 2). Type of blood-flow pathology was also registered as unifocal, multifocal (2–5 areas) and generalized ("patchy" pattern).

Statistical Methods

Independent samples were analyzed by means of the Mann-Whitney *U*-test, proportions were compared using the Fisher exact test, and the Spearman rank correlation test was used in calculating correlations.

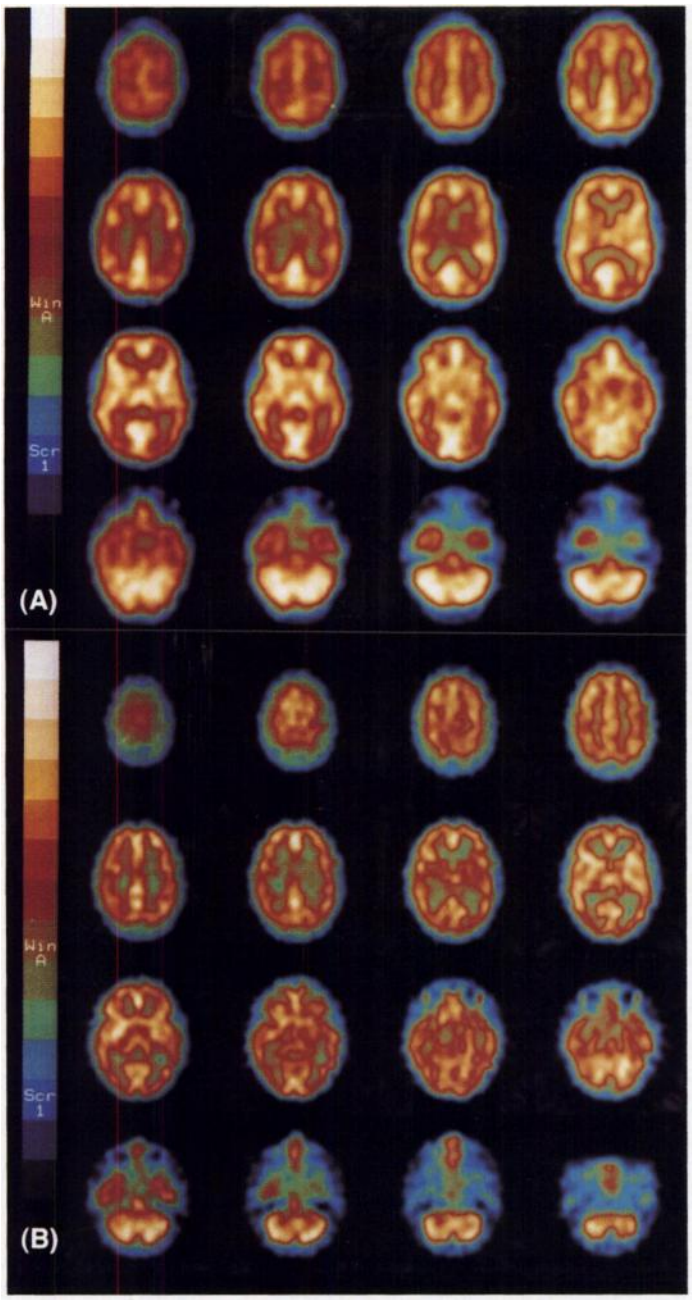

FIGURE 2. Transaxial slices (SPECT) in two patients with aseptic meningoencephalitis. (A) Woman (19 yr) with HSV 2 meningitis and cognitive dysfunction (decreased concentration) examined 39 days after onset. Normal rCBF. (B) Male (17 yr) with enteroviral disease (echo 30), with no remaining neurological or cognitive symptoms, examined 35 days after onset. Decreased rCBF with generally patchy pattern bilateral (flow rate 1).

The study was approved by the local ethical committee.

RESULTS

Acute Stage of Disease

Regardless of the cause, 64 of 129 patients (50%) with aseptic meningoencephalitis showed pathological changes with decreased rCBF at first examination after a median of 6 wk in the acute stage of disease. Reduction of rCBF was significantly more frequent in males than in females, 42 of 60 and 22 of 69, respectively ($p < 0.0001$). This difference was independent of etiology (TBE, $p = 0.005$; non-TBE, $p < 0.001$). The rate of decrease in rCBF was also significantly higher in males than in females ($p < 0.0001$). Among patients with TBE, 36 of 73 (49%) showed disturbed cerebral perfusion compared to 28 of 56 (50%) in non-TBE. Decreased rCBF was significantly ($p = 0.02$) more frequent in patients with encephalitis (27 of 44, 61%) than in patients with meningitis (37 of 85, 44%). Otherwise, reduced rCBF did not appear to depend on the severity of disease in any diagnostic group. In the subgroup of patients with reduced rCBF, slight-to-moderate decrease in rCBF was seen in 36 of 73 (49%) TBE patients who had not recovered and in 7 of 13 (54%) patients who had recovered at Week 6. The corresponding figure in non-TBE patients was 16 of 30 (53%) and 12 of 26 (46%), respectively (Table 1). Moderate-to-severe decrease in rCBF was seen in only 18% and 11% of the TBE and non-TBE patients, respectively, at 6 wk. The only patient who showed severe decrease in rCBF after 6 wk had HSV 1 meningoencephalitis. There was no correlation between clinical outcome and patients with moderate decrease in rCBF ($n = 19$) in any diagnostic group. Enteroviral meningoencephalitis resulted in pathological changes in 11 of 24 (46%) patients and HSV 2 in only 2 of 9 (22%) patients after 6 wk. Pathological perfusion was seen in 13 of 21 (62%) patients with unknown cause.

In all diagnoses, the localization of perfusion defects was predominantly general/patchy (Figs. 1 and 2) or multifocal. Among these there were no significant differences between the TBE (28 of 73, 38%) and non-TBE (24 of 56, 43%) groups (Table 2). Unifocal changes were found in 8 of 73 (11%) of the TBE patients and 4 of 56 (7%) of non-TBE patients. Bilateral changes were found in 26 of 73 (36%) of the TBE patients and in 21 of 56 (38%) of non-TBE patients.

Both groups showed a dominance for left-sided localization when the change was unifocal, 7 of 10 and 5 of 7 patients, respectively. Focal changes were frontoparietal, parietal or temporal in a majority of the patients without generally distributed flow disturbances, 15 of 73 TBE (21%) and 10 of 56 non-TBE (18%) patients (Table 3).

rCBF patterns in patients with cognitive dysfunction after Week 6 did not differ from those of other patients.

Long-Term, 1-Yr Follow-Up

After 1 yr, 19 patients out of 109 (17%) showed worsening of their pathological rCBF (Table 4). There was a significant positive correlation in TBE between age and pathological rCBF ($p = 0.002$; $r_s = 0.45$). This correlation was not reproduced after 6 wk. Also, 28 of 109 (26%) patients had improvement of rCBF decrease. Decreased rCBF was more commonly seen in males than in females ($p = 0.003$), together with higher rates of flow reduction ($p = 0.001$; TBE, $p = 0.04$ and non-TBE, $p = 0.03$).

In the subgroup of patients with worsening of rCBF pathology ($n = 19$), worsening was more common in TBE patients not recovered (11 of 11) than in non-TBE patients with symptoms remaining at Week 6 (4 of 8, $p = 0.01$). After 1 yr there was no association between remaining symptoms and worsening of rCBF decrease (Table 4). Twenty-nine of 62 TBE patients and 21 of 46 non-TBE patients had pathological perfusion at long-term follow-up. Worsening was noticed after 1 yr in 7 of 33 (21%) TBE patients with normal rCBF after 6 wk. The corresponding figures in non-TBE patients were 6 of 26 (23%). There was no obvious alteration in localization of perfusion changes in the brain regardless of cause. Only 8% and 9% of TBE and non-TBE patients, respectively, had moderate decreases in rCBF.

Worsening of perfusion disturbances after 1 yr did not correlate with the intensity of meningoencephalitis on admission to the hospital (Table 4). Worsening of blood-flow disturbances was connected to remaining symptoms after 6 wk in TBE patients but not in any other group of patients with

TABLE 1
Cerebral Blood Flow (CBF) in Patients with Tick-Borne Encephalitis (TBE) and Aseptic Meningoencephalitis of Other Cause Related to Clinical Status on Admission and at Follow-up

Clinical status on admission	CBF*	Week 6 (median 45.5 days; 26–196) No. of patients (%) TBE (n = 73) NR (n = 60)	TBE (n = 73) R (n = 13)	Non-TBE (n = 56) NR (n = 30)	Non-TBE (n = 56) R (n = 26)	1 yr (median 13 mo; 11–17) No. of patients (%) TBE (n = 62) NR (n = 28)	TBE (n = 62) R (n = 34)	Non-TBE (n = 47) NR (n = 12)	Non-TBE (n = 47) R (n = 35)
Meningitis†	2–3	4 (7)	2 (15)	4 (13)	1 (4)	0 (0)	1 (3)	0 (0)	3 (9)
	1	9 (15)	1 (8)	7 (23)	9 (35)	7 (25)	9 (27)	3 (25)	11 (31)
	0	17 (28)	4 (31)	13 (43)	14 (54)	4 (14)	10 (29)	5 (42)	19 (54)
Encephalitis†	2–3	4 (7)	3 (23)	0 (0)	1 (4)	1 (4)	3 (9)	1 (8)	0 (0)
	1	12 (20)	1 (8)	5 (17)	1 (4)	5 (18)	3 (9)	2 (17)	1 (3)
	0	14 (23)	2 (15)	1 (8)	0 (0)	11 (39)	8 (24)	1 (8)	1 (3)
Total	2–3	8 (13)	5 (39)	4 (13)	2 (8)	1 (4)	4 (12)	1 (8)	3 (9)
	1	21 (35)	2 (15)	12 (40)	10 (39)	12 (43)	12 (35)	5 (42)	12 (34)
	0	31 (52)	6 (46)	14 (47)	14 (54)	15 (54)	18 (53)	6 (50)	20 (57)

*Rating score: 0 = normal, 1 = slight decrease, 2–3 = moderate decrease to severe decrease.
†Meningitis = mild disease, encephalitis = moderate-to-severe disease.
NR = not recovered; R = recovered.

established diagnoses. Clinical status at follow-up after 1 yr was not associated with worsening of decreased rCBF according to diagnosis (Table 5).

TBE patients with spinal nerve paralysis did not show a pattern different from patients without. In acute Stage 4, 9 patients had pathological rCBF. One patient showed worsening and another improvement after 1 yr. An unchanged pattern was found in 6 patients with spinal nerve paralysis.

No areas of increased cerebral blood flow were disclosed, either in the subacute stage or at long-term follow-up. No detectable flow changes were found in the cerebellum.

DISCUSSION

Regional blood flow was studied in patients with aseptic meningoencephalitis of different causes in a prospective study with special focus on TBE. The TBE patients were randomly selected from a prospective group. After the initial investigation, 18% of patients (15% TBE and 16% non-TBE) refused further participation in the study. However, their clinical status in acute stage of disease or after 1 yr did not cause any bias in the evaluation. Decreased cerebral blood flow was seen in half of the patients after 6 wk. Significantly more patients with predominantly encephalitis had reduced rCBF than did patients with meningitis. After 1 yr, 46% of patients had reduced rCBF. In most cases the decrease in rCBF was slight but was moderate in 18% and 11% at 6 wk and in 8% and 9% at 1 yr in patients with TBE and non-TBE, respectively. Only 1 patient, with HSV-1 encephalitis, had a severe decrease in rCBF.

rCBF scintigraphy with SPECT is a highly sensitive method for disclosing cerebral perfusion pathology. In HIV-infected patients without neurological deficits, SPECT has shown blood-flow pathology, whereas other investigations with CT and MRI show normal findings (*23*). Reduced rCBF is associated with AIDS dementia complex (*21*). A connection to decreased rCBF in Alzheimer's dementia has also been established (*15*). Blood-flow scintigraphy using gamma camera and SPECT has proved to correlate well with flow studies using PET (*14,17*). SPECT has been used in meningoencephalitis mainly in pediatric cases (*16,19,20*) and HSV encephalitis (*25,26,38*). In the latter disease, loss of brain substance primarily correlates with absent blood flow in one temporal region (or lobe) with initial hyperperfusion and later a decrease of blood flow. Otherwise the knowledge of flow disturbances in adult patients with

TABLE 2
Focal Distribution of Regional Cerebral Blood Flow (rCBF) in Patients with TBE and Aseptic Meningoencephalitis of Other Etiology, Acute and at Follow-Up in Relation to Clinical Status on Admission

Clinical status on admission	F*	Week 6 (median 45.5 days; 26–196) No. of patients TBE NR (n = 60)	TBE R (n = 13)	Non-TBE NR (n = 30)	Non-TBE R (n = 26)	1 yr (median 13 months; 11–17) No. of patients TBE NR (n = 28)	TBE R (n = 34)	Non-TBE NR (n = 12)	Non-TBE R (n = 35)
Meningitis	P	4	3	2	4	3	3	—	5
	M	7	—	7	5	3	5	2	4
	U	2	—	2	1	1	2	1	5
Encephalitis	P	5	1	3	1	2	3	—	1
	M	7	1	1	1	2	1	2	—
	U	4	2	1	—	2	2	1	—
Total	P	9	4	5	5	5	6	—	6
	M	14	1	8	6	5	6	4	4
	U	6	2	3	1	3	4	2	5

*Focality: U = unifocal, M = multifocal (2–5), P = patchy (>5 in both hemispheres).
NR = not recovered; R = recovered.

TABLE 3
Localization of Regional Cerebral Blood Flow (rCBF) and Blood-Flow Rating in Acute Stage of Disease at 1-Yr Follow-Up in Patients with Tick-Borne Encephalitis (TBE) and Other Aseptic Meningitis

Localization	rCBF*	Week 6 (median 45.5 days; 26–196) No. of patients		1 yr (median 13 mo; 11–17) No. of patients	
		TBE	Non-TBE	TBE	Non-TBE
Frontal	1	2	—	2	1
	2–3	—	—	—	—
Frontoparietal	1	3	1	1	—
	2–3	2	—	1	—
Frontotemporal	1	1	—	—	—
	2–3	—	—	—	—
Parietal	1	1	3	2	4
	2–3	2	1	1	—
Temporal	1	6	4	6	3
	2–3	1	1	—	1
General	1	9	8	10	4
	2–3	5	3	3	3
Nonfocal	0	42	36	35	31

*Rating score: 0 = normal, 1 = slight decrease, 2 = moderate decrease, 3 = severe decrease.

aseptic meningoencephalitis is limited. In this study no differences were noticed between TBE and non-TBE in acute stage of disease after a median of 6 wk, although worsening of decreased rCBF was significantly more common in TBE patients with remaining neurological symptoms than in non-TBE patients. Persisting defects in rCBF were seen irrespective of cause after 1 yr. In patients with reduced rCBF, a more generally disturbed pattern of cerebral blood flow could be seen in TBE than in non-TBE. However, the patchy distributed blood flow did not correlate to focal neurological signs or cognitive dysfunction. Reduction of rCBF may be due to cortical atrophy, decreased metabolism in normal neurons or normal metabolism in neurons with dysfunction (*17*). Furthermore, reduced uptake of the radiopharmaceutical could be related to a disturbed metabolic retention in pathologic brain tissue, rather than to reduced cerebral blood flow (*14*).

Vasculitis and severe CNS inflammation are parts of the pathophysiology in TBE. The inflammatory reaction did not seem to cause a long-lasting decrease in rCBF followed by neurological dysfunction. Focal areas with increased blood flow were not detected in this study, but hyperfixation and increased perfusion without MRI findings, as in HSV encephalitis (*24,27*), may have occurred before the time of this study. However, in 1 patient not included in the study, a severe increase of right temporal lobe perfusion was seen at Day 10 of HSV encephalitis. At Week 7 of disease SPECT showed less, but still increased, hyperperfusion followed by a severe decrease of right temporal lobe rCBF at 1 yr of disease (Sköldenberg et al., unpublished data). Recently, intracerebral damage was demonstrated with MRI in one lethal TBE case (*39*). However, we could not show any loss of brain substance or other pathological findings, as in HSV encephalitis, in the 10 TBE patients examined with MRI.

This study showed that decreased cerebral perfusion is related to aseptic meningoencephalitis of all causes, but not exclusively related to clinical course or outcome. Mild initial decrease in rCBF was associated with the persistence of neurological symptoms in TBE, and SPECT may be used to

TABLE 4
Changes in Regional Cerebral Blood Flow (rCBF) in Patients with Tick-Borne Encephalitis (TBE) and Aseptic Meningoencephalitis of Other Cause at 1-Yr Follow-Up Related to Clinical Status on Admission

Clinical status on admission	rCBF	1 yr (median 13 mo; 11–17) No. of patients (%)			
		TBE		Non-TBE	
		NR (n = 28)	R (n = 34)	NR (n = 12)	R (n = 35)
Meningitis*	Improvement	3 (11)	5 (15)	1 (8)	10 (29)
	Worsening	4 (14)	3 (9)	2 (17)	5 (14)
	Unchanged decrease	1 (4)	2 (6)	1 (8)	6 (17)
	Unchanged normal	3 (11)	10 (29)	4 (33)	11 (31)
Encephalitis*	Improvement	5 (18)	2 (6)	1 (8)	1 (3)
	Worsening	2 (7)	2 (6)	1 (8)	—
	Unchanged decrease	3 (11)	4 (12)	1 (8)	1 (3)
	Unchanged normal	7 (25)	6 (18)	1 (8)	—
Total	Improvement	8 (29)	7 (21)	2 (17)	11 (31)
	Worsening	6 (21)	5 (15)	3 (25)	5 (14)
	Unchanged decrease	4 (14)	6 (18)	2 (17)	7 (19)
	Unchanged normal	10 (36)	16 (47)	5 (42)	12 (34)

*Meningitis = mild disease, encephalitis = moderate-to-severe disease.
NR = not recovered; R = recovered.

TABLE 5
Changes in Regional Cerebral Blood Flow (rCBF) in Patients with Tick-Borne Encephalitis (TBE) and Aseptic Meningoencephalitis of Other Cause Between Acute Stage and Long-Term Follow-Up Related to Clinical Status at Follow-Up

	1 yr (median 13 mo; 11–17)							
	Not recovered				Recovered			
Diagnosis	I	W	U^+	U^-	I	W	U^+	U^-
TBE (n = 62)	8	6	4	10	7	5	6	16
Enteroviral disease (n = 21)	—	2	1	1	4	3	5	5
Herpes simplex type 2 (n = 8)	—	—	—	3	1	1	—	3
Herpes simplex type 1 (n = 1)	—	—	1	—	—	—	—	—
CMV (n = 1)	—	—	—	—	—	—	1	—
Unknown cause (n = 16)	2	—	1	1	6	1	1	4

I = improvement; W = worsening; U^+ = unchanged decreased rCBF; U^- = unchanged normal rCBF; CMV = cytomegalovirus.

verify the clinical status. Paralysis of spinal nerves in TBE patients did not affect the cerebral blood flow in any particular direction, indicating radiculitis or myelitis rather than CNS involvement. Worsening was seen in one-fourth of TBE patients without connection to outcome after 1 yr.

The significance of reduced rCBF is still obscure. The validity and reliability of the rCBF pathology detected in this study may be questioned. No semiquantitative analysis has been used, and the focal flow disturbances described were often small. SPECT was also performed with a single-head gamma camera giving lower spatial resolution than the more frequently used dual- or triple-head gamma cameras. Finally, the high sensitivity of the method could cause interpretation bias regarding normal flow variants or age-dependent flow alterations (*14*). However, studies using visual interpretation of rCBF with SPECT and single-head gamma cameras have been widely accepted in the vast scientific literature appearing during the past decade. Furthermore, in this study no increase in detected flow pathology was seen with increasing age.

The methodological strengths of this study are the long-term follow-up (i.e., each patient becomes his or her own control) and the fact that flow studies of the same patient were simultaneously displayed on the computer screen when visually evaluated (*15*). Current data on pathology of cerebral blood flow by SPECT in patients with TBE or other acute meningoencephalitis need to be analyzed in relation to corresponding data from functional neuropsychometric tests.

CONCLUSION

SPECT is useful in detecting rCBF changes in patients with aseptic meningoencephalitis, especially when encephalitis is predominant. In TBE patients, remaining neurological symptoms after 6 wk of disease were associated with worsening of decreased rCBF. Surprisingly, this difference was equalized at 1-yr follow-up with no connection to the clinical course or persisting neurological dysfunction. The clinical use of SPECT in predicting outcome and long-term sequelae in aseptic meningoencephalitis, e.g., TBE, seems limited.

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Carbon-11-NNC 112: A Radioligand for PET Examination of Striatal and Neocortical D_1-Dopamine Receptors

Christer Halldin, Christian Foged, Yuan-Hwa Chou, Per Karlsson, Carl-Gunnar Swahn, Johan Sandell, Göran Sedvall and Lars Farde

Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, Stockholm, Sweden; and Novo Nordisk A/S, Måløv, Denmark

The aim of this work was to explore the potential of a selective D_1-dopamine receptor antagonist as a new radioligand for PET examination of striatal and neocortical D_1-dopamine receptors. **Methods:** The active (+)- and inactive (−)-enantiomers of [^{11}C]NNC 112 were radiolabeled using the N-methylation approach and were examined by PET in cynomolgus monkeys and healthy men. Metabolite levels in plasma were measured by gradient high-performance liquid chromatography (HPLC). **Results:** N-methylation of the corresponding desmethyl precursors with [^{11}C]methyl triflate gave high total radiochemical yield (50%–60%) and specific radioactivity (110 GBq/μmol). (+)-[^{11}C]NNC 112 binding in cynomolgus monkeys was 5.77 ± 0.31 and 2.36 ± 0.14 times higher in the striatum and neocortex, respectively, than in the cerebellum at a transient equilibrium that appeared 40–50 min after injection. The binding of (+)-[^{11}C]NNC 112 is stereoselective, because the brain distribution of the inactive (−)-enantiomer was on an equally low level for all brain regions. Displacement and pretreatment experiments using unlabeled SCH 23390 and ketanserin confirms that (+)-[^{11}C]NNC 112 binds specifically and reversibly to D_1-dopamine receptors. The radioactivity ratios of the striatum, frontal cortex and nucleus accumbens to the cerebellum were 3.8–4.0, 1.7–2.0 and 2.8–3.1, respectively, at a transient equilibrium that appeared 40–50 min after injection in four healthy human subjects. Linear graphical analysis gave distribution volume ratios of 3.9 and 1.5 in the putamen and frontal cortex, respectively. The fraction of the total radioactivity in human plasma representing unchanged (+)-[^{11}C]NNC 112 was 85% at 5 min and 25% at 75 min after injection. **Conclusion:** (+)-[^{11}C]NNC 112 should be a useful PET radioligand for quantitative examination of not only striatal but neocortical D_1-dopamine receptors in man.

Key Words: brain; D_1-dopamine receptors; striatal; neocortical; extrastriatal; NNC 112; carbon-11; PET

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For correspondence or reprints contact: Christer Halldin, PhD, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, S-17176 Stockholm, Sweden.

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PET and the radioligand [^{11}C]SCH 23390 have been used to examine D_1-like dopamine receptors (D_1R) in the monkey and human brain (*1–5*). There is a high density of D_1R in the basal ganglia and also in the neocortex. The neocortical density is about 30% of that in the striatum as determined in vitro and in vivo (*6,7*).

Studies on brain morphology, biochemistry and physiology indicate that the function of extrastriatal brain regions may be disturbed in patients with schizophrenia (*8*). In a recent PET study, Okubo et al. (*9*) found a reduction in D_1R binding in the prefrontal cortex of patients with schizophrenia. The reduction was significantly correlated to negative symptoms.

A problem in using [^{11}C]SCH 23390 is that the neocortex-to-cerebellum ratio is lower than 1.5, which is not ideal for detailed quantitative examination of D_1R in the neocortex (*1*). It is important to develop a selective PET radioligand that provides a high signal-to-noise ratio in the neocortical brain region.

(+)-NNC 112 is a new benzazepine ((+)−8-chloro-5-(7-benzofuranyl)−7-hydroxy-3-methyl-2,3,4,5-tetra-hydro-1H-3-benzazepine, Fig. 1) that has high affinity for D_1R, 100-fold lower affinity for 5-HT_{2A}, and virtually no affinity for other putative central receptors (Tables 1 and 2) (*10–12*). In vivo binding studies in rodents have demonstrated that the behavioral and biochemical effects of NNC 112 are closely correlated with the D_1R occupancy (*10*).

The aim of this study was to develop the selective D_1R antagonist (+)-[^{11}C]NNC 112 as a new radioligand for PET. Stereoselectivity was examined with the two enantiomers of [^{11}C]NNC 112. The specificity of binding was examined by displacement and pretreatment experiments. Radioligand me-