Decreased Brain Glucose Utilization in Patients with Cushing's Disease

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Glucocorticoid hormones affect glucose use in different tissues, and the results of several experimental studies have suggested that glucocorticoids have a central action on cerebral metabolism. PET, using the radiotracer ^{18}F-fluorodeoxyglucose (FDG), permits the measurement of cerebral glucose metabolism. **Methods:** To investigate whether cerebral glucose metabolism would be altered in patients with increased plasma glucocorticoid levels, we analyzed the FDG PET studies that were done on 13 patients with Cushing's disease and compared the results with those obtained in 13 age-matched normal control subjects. A second FDG PET scan was performed on 4 patients after surgical removal of the pituitary adenoma. **Results:** Patients with Cushing's disease had a significant reduction in cerebral glucose metabolism compared with normal controls. In the patients on whom a second PET scan was performed, there was a trend toward increased glucose metabolism on the second scan when comparing pre- and postsurgery values for each patient. **Conclusion:** We suggest that the decreased cerebral glucose metabolism we observed in Cushing's disease is attributable to increased glucocorticoid levels, and we speculate that abnormal cerebral glucose metabolism might contribute to the cognitive and psychiatric abnormalities that are frequently observed in patients with Cushing's disease.

Key Words: Cushing's disease; cerebral glucose metabolism; PET; glucocorticoids

J Nucl Med 1998; 39:786–790

Cushing's disease is caused by prolonged exposure to elevated plasma glucocorticoids (GCs) due to increased secretion of adrenocorticotropic hormone (ACTH) from a pituitary ACTH-producing adenoma (1,2). Neurological and psychiatric abnormalities are commonly associated with Cushing's disease and include depression, which is the most frequent psychiatric abnormality, as well as mild behavioral and cognitive disturbances and psychoses (3,4). PET, using ^{18}F-fluorodeoxyglucose (FDG), has been used extensively to characterize abnormalities of glucose metabolism in neurological and psychiatric conditions (5). Adrenal GCs are known to affect cellular glucose metabolism in the body (6) and the brain (7). Thus, we hypothesized that patients with Cushing's disease might have a reduction in cerebral glucose metabolism compared with normal people. Therefore, we used FDG PET to measure cerebral glucose metabolic rates in 13 patients with Cushing's disease and compared these results with values obtained in a group of age-matched healthy individuals.

MATERIALS AND METHODS

The PET studies were performed under approved National Institutes of Health protocols. Patients and healthy participants

gave informed consent after thorough explanation of the procedures. Thirteen patients (4 men, 9 women; mean age 40 yr; range 26–62 yr) with ACTH-secreting pituitary adenomas and Cushing's disease and 13 age-matched healthy participants (7 men, 6 women; mean age 40.5 yr; range 22–62 yr) studied with the same equipment and acquisition protocol were included in the study. All patients were participating in a prospective study to assess the diagnostic potential of FDG PET in detecting pituitary adenomas (8). In addition, a second FDG PET scan was performed on 4 patients 3–4 mo after surgery.

Patient details and laboratory findings are shown in Table 1. The diagnosis of Cushing's disease was made for all patients on the basis of clinical evaluation, standard laboratory tests and inferior petrosal venous sinus sampling for the measurement of ACTH levels (9,10). The diagnosis was confirmed by pathological examination of specimens after transsphenoidal surgical removal of the pituitary adenoma. The diagnostic workup included pre- and postcontrast MRI with a 1.5-T imager (General Electric, Milwaukee, WI).

FDG PET studies were performed on the NIH-designed Neuro-PET scanner (11) (in-plane resolution 6–7 mm; longitudinal axis resolution 11 mm) 35–45 min after intravenous administration of 185 MBq FDG after at least 6 hr of fasting. Studies were conducted in standard conditions of sensory deprivation with eyes and ears covered in a dimly lit room. The scanning plane was parallel to the cantho-meatal line. Cerebral metabolic rates for glucose (CMR$_{glu}$) were calculated according to Sokoloff's model (12) using a simplified operational equation (13) with standard rate and lumped constants (14,15) and a tracer input function derived from blood samples obtained at timed intervals from a heated hand vein. PET data processing included a standard correction for scatter and random coincidences. The attenuation correction was calculated from the outline of the visible skull. Regional analysis of CMR$_{glu}$ was performed by one of us on a standard series of PET images using a template of circular (8 mm in diameter) regions of interest (ROIs) positioned on the brain cortex (frontal, parietal, temporal and occipital), striatum (caudate nucleus and putamen), thalamus and cerebellum, as described in a previous article (16). Average CMR$_{glu}$ were calculated for each anatomic area. Mean regional CMR$_{glu}$ were finally obtained and compared in the two groups. Possible correlations between CMR$_{glu}$ and clinical and laboratory variables including age, sex, preoperative urinary free cortisol, 17-hydroxycorticosteroid (17-OHCS), plasma cortisol, duration of symptoms, severity of disease and psychiatric symptoms also were analyzed.

Statistical analysis was performed using Wilcoxon's rank correlation test for comparison of CMR$_{glu}$ between the two groups (p < 0.01). Linear regression analysis was used to assess possible correlations between CMR$_{glu}$ and 17-OHCS, urinary free cortisol and duration of symptoms. Regional CMR$_{glu}$ before and after

TABLE 1
Clinical and Laboratory Patient Data

	Patient no.												
Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (yr)	45	48	27	53	26	27	34	43	36	48	40	62	32
Sex	F	M	F	F	F	F	F	M	F	M	F	M	F
Urinary free cortisol (μg/24 hr; normal values 20–90)	121	180	360	604	289	265	336	239	182	138	148	259	122
17-OHCS (mg/24 hr; normal values 3–10)	17.1	27.4	18.1	26.8	25.9	10.2	7.2	26.1	16.2	14.9	10.6	15.7	16.3
Serum creatinine (mg/dl; normal values <1.5)	1.22	1.5	1.4	1.03	1.28	1.28	0.92	1.24	1.37	1.08	1.27	1.49	1.54
17-OHCS/serum creatinine (normal ratio 2–6)	14.0	18.3	12.9	26.0	20.2	8.0	7.8	21.0	11.8	13.8	8.3	10.5	10.6
Plasma cortisol (μg/dl; normal values 5–20)	17.5	19.4	23.9	21.5	15.6	12.6	18.6	17	25.8	13.4	22.1	17.4	29.7
a.m./p.m. variation plasma cortisol (6–8 a.m./11 a.m.–1 p.m. values)	26.4/ 12.9	35.2/ 23.7	24.9/ 22.2	30.7/ 24.2	23.2/ 15.1	na	17.8/ 14.5	23.9/ 22.7	24.4/ 21.2	31.7/ 21.5	14.4/ 25.4	22.9/ 20	33.8/ 30.9
Duration of symptoms (yr)	12	3	2	1	4	1	1	2	5	2	>5	10	4
Psychiatric symptoms	L	D, I	I	L, I	D, L, I	D, L	na	na	na	D	L	na	D, L
Plasma glucose (mg/dl; normal values 70–120)	98.3	96.3	86.5	102	85.6	114	86.6	95.8	104	97.7	112	92.5	88.6
Petrosal sinus sampling	+	+	+	+	+	+	+	na	+	+	+	+	+
Cerebral atrophy	no	no	no	no	no	no	no	no	no	yes*	no	no	no

*Focal dilatation of left parietal subarachnoidal spaces.
17-OHCS = 17-hydroxycorticosteroid; D = depression; L = lability; I = insomnia; na = not available; + = positive.

surgery were compared using a Student's t-test for paired values (p < 0.05).

RESULTS

In patients with Cushing's disease, regional analysis showed that CMR_{glu} values were significantly lower in all brain regions except the striatum (caudate nucleus and putamen) compared with healthy participants (p < 0.01). Regional glucose metabolic rates for each individual in the two groups are presented in scatterplot format in Figure 1. The degree of variability in the measurements obtained for each anatomical area was assessed by determining the average coefficient of variation (s.d. of ROI values/mean ROI values) for a particular region in each individual. On average, this was 10 ± 3% (mean ± s.d.) of the mean regional CMR_{glu} values observed.

In the patients on whom a second FDG PET scan was performed after surgery, there was a tendency for a global increase in glucose metabolism in the follow-up study, when values for each patient were analyzed individually (Figs. 2 and 3). However, statistical analysis of the regional changes in
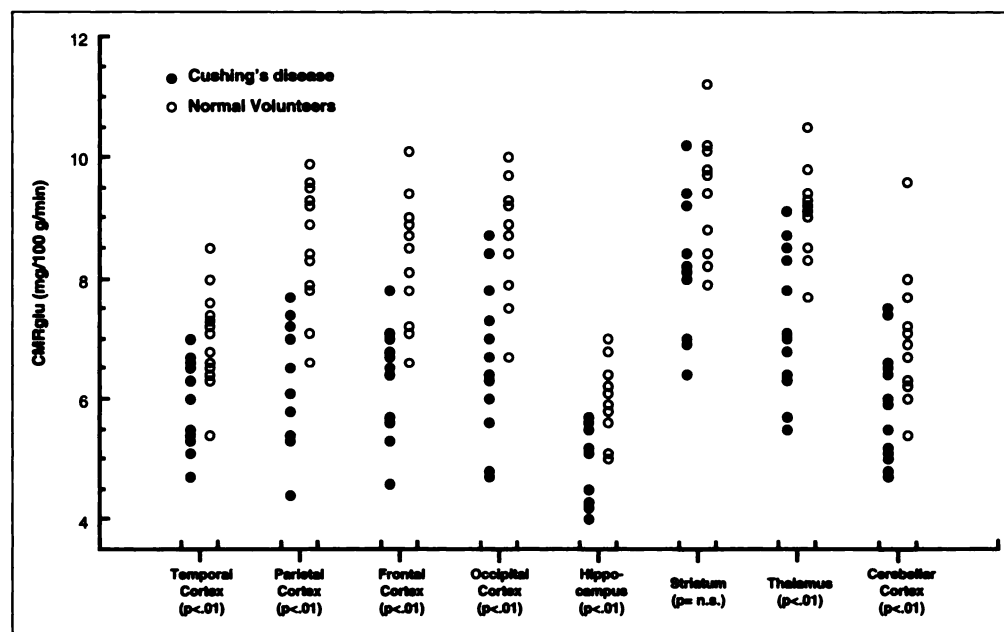

FIGURE 1. Scatterplot presentation of regional CMR_{glu} values in patients with Cushing's disease and in healthy volunteers in the regions studied. Values are significantly lower (p < 0.01) for patients with Cushing's disease in all regions except the striatum (p = n.s.).
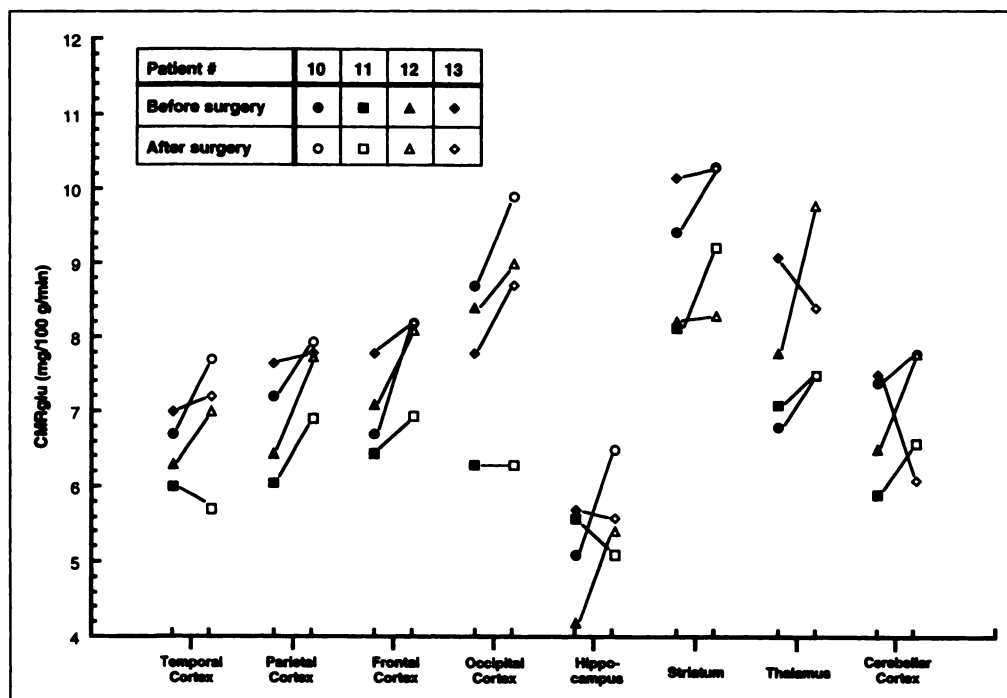
FIGURE 2. Comparison of CMR_{glu} values in all regions studied in patients who had FDG PET studies done before and after removal of the ACTH-producing pituitary adenoma (Patients 10–13). The solid lines connect values obtained from the same patient before and after surgery.

CMR_{glu} in these four patients showed a significant increase in glucose metabolism only in the frontal lobe (p = 0.044). Postsurgery laboratory findings are presented in Table 2. No statistically significant correlation was observed between CMR_{glu} and the clinical and laboratory parameters considered (i.e., duration of symptoms, 17-OHCS and urinary free cortisol).

DISCUSSION

In Cushing's disease, our results indicate that there is a generalized reduction in cerebral glucose metabolism. We suggest that this glucose hypometabolism is secondary to chronic elevation of plasma GC levels and that it may contrib-

FIGURE 3. Patient 12: A 62-yr-old man with a 10-yr history of Cushing's disease. Transaxial FDG PET images at the level of the basal ganglia are shown. Studies were acquired 2 days before (left) and 126 days after (right) transsphenoidal surgery. Images are displayed with an identical scale for CMR_{glu} (values are mg glucose/100 g tissue/min). A global increase in CMR_{glu} is evident after surgery.

ute to the neuropsychiatric abnormalities observed in the disease (3,4). This central action of GCs also is suggested by the observation of psychiatric abnormalities in patients with Cushing's syndrome attributable to adrenal adenomas (17). However, a definite correlation between plasma cortisol levels and the severity of the psychiatric disturbances has not been clearly defined (18,19). Our findings are further supported by our recent observation that there is global cerebral glucose hypometabolism in patients with brain tumors who are taking exogenous corticosteroids (dexamethasone) for the control of cerebral edema (16).

In this study, there were more men in the control population; indeed, age-matched controls were selected because there was limited availability of sex-matched patients studied with the same equipment and procedure. However, the preponderance of male controls could have only negatively affected the differentiation of healthy participants from Cushing's patients because healthy women usually have higher regional CMR_{glu} values (20).

There are several lines of evidence to support the central action of GCs on glucose metabolism. GCs affect glucose uptake and metabolism throughout the body (6) and easily cross the blood-brain barrier (21). Kadekaro et al. (7) showed indirectly that there is a central effect of GCs because they found increased cerebral glucose metabolism in adrenalectomized rats. Horner et al. (22) showed that corticosterone and dexamethasone inhibit glucose uptake by cultured hippocampal neurons and glia in a dose-dependent, receptor-mediated fashion. In addition, the results of several studies in experimental animals have suggested that there is a selective action of GCs on the hippocampus and that the neuropsychiatric features of Cushing's disease could be related to hippocampal functional abnormalities (23,24). However, our results indicate that there was a generalized reduction in glucose metabolism rather than a selective regional effect in the region of the hippocampus. Possible explanations for the difference in our data from that in animal studies include the following:
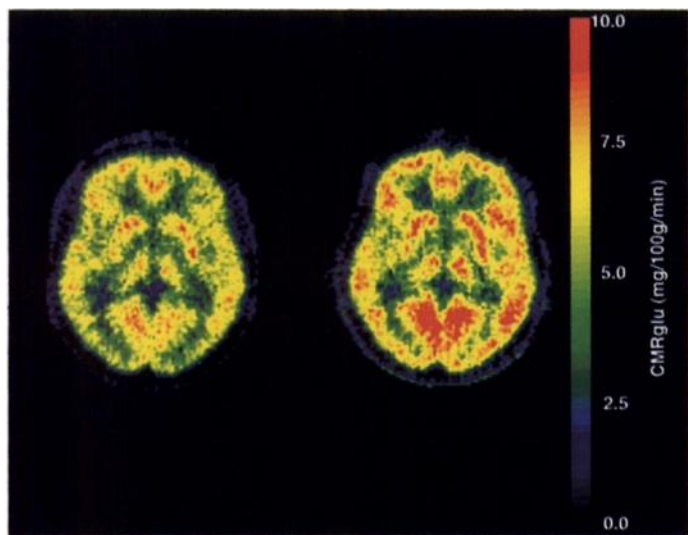
TABLE 2
Clinical and Laboratory Patient Data Postsurgery

	Patient no.			
Variable	10	11	12	13
Age (yr)	48	40	62	32
Sex	M	F	M	F
Urinary free cortisol (μg/24 hr; normal values 20–90)	10.0	11.0	10.0	19.0
17-OHCS (mg/24 hr; normal values 3–10)	na	4.9	4.2	na
Plasma cortisol (μg/dl; normal values 5–20)	1.2	3.1	<1	15.0
Days after surgery	90	86	126	99
Plasma glucose (mg/dl; normal values 70–120)	88.7	138.5	91.5	84.6

17-OHCS = 17-hydroxycorticosteroid; na = not available.

1. The hippocampus is a small structure and the resolution of the PET device used in this study was such that partial volume errors may have limited the detection of a more marked reduction in hippocampal glucose use than in other cerebral regions.
2. There may be a difference in the responses of the human and animal brains to GC.
3. The widespread distribution of GC receptors in glia and neurons could account for a generalized metabolic effect (25,26).
4. There may be a direct in vivo effect of cortisol on endothelial transport of glucose (27). In cultured human fibroblasts, dexamethasone causes translocation of glucose transporter proteins from the plasma membrane to an intracellular compartment (28), which may reduce glucose transport. Although values for CMR_{glu} that are calculated with the Sokoloff method remain stable for a wide range of transfer rate values (29), we cannot exclude the possibility that the glucose hypometabolism that we found reflects reduced glucose transport.

Another factor that may affect the estimation of CMR_{glu} is partial volume averaging, that is, variable fractions of brain parenchyma (gray and white matter) and cerebrospinal fluid (CSF) are included in the volumes evaluated with ROI analysis. In cases of brain atrophy, one must watch for (and possibly try to correct) underestimations of CMR_{glu} due to the inclusion of ametabolic CSF in the ROIs. Cerebral atrophy has been described in patients with Cushing's disease (30) and after chronic steroid (31) and ACTH administration (32). However, none of our patients (Table 1) had evidence of diffuse brain atrophy on MR images.

The small number of patients who had an FDG PET scan performed after surgery did not allow us to draw definitive conclusions about global and regional changes in CMR_{glu} after remission of hypercortisolism. Furthermore, the follow-up studies were performed 86–126 days after surgery (Table 2), which may not be long enough to adequately determine the degree of recovery of CMR_{glu} values. However, our results indicate a trend toward global reversal of the cerebral metabolic abnormalities after surgery (Figs. 2 and 3).

The association between affective disorders and GC disregulation is particularly intriguing because brain metabolic and perfusion abnormalities have been described in patients with depression, in the resting state, with both PET and SPECT. Baxter et al. (33) reported regional reductions and asymmetry in glucose metabolism as well as abnormal anteroposterior

gradients and basal ganglia to cortex ratios with FDG PET. Silfverskiold et al. (34) and Uytendhoef et al. (35) found regional abnormalities of cerebral blood flow in different subgroups of patients. It is tempting to speculate that the hypercortisolism associated with depression might underlie these abnormalities. All our patients received a routine neurological and psychiatric assessment, but detailed neuropsychological tests were not performed because the main aims of the clinical protocol were the diagnosis and appropriate treatment of Cushing's disease. Thus, we could not correlate our metabolic observations with neuropsychological parameters. We did not observe a correlation between CMR_{glu} and the degree of hypercortisolism measured by urinary free cortisol and 17-OHCS, which suggests that the decreased CMR_{glu} in Cushing's disease may reflect a combination of the duration and degree of exposure to hypercortisolism rather than the clinical and laboratory status at the time of the PET study.

CONCLUSION

We observed a generalized decrease in cerebral glucose metabolism in patients with Cushing's disease. Our data suggest that chronically increased plasma GC levels affect CMR_{glu}. Our results offer some evidence for the effects of GCs on the brain and suggest the need for prospective studies in patients with Cushing's disease and in those receiving long-term GC treatment.

REFERENCES

1. Nelson DH. Cushing's syndrome. In: DeGroot LJ, ed. *Endocrinology*. Philadelphia: Saunders; 1989:1660–1675.
2. Besser GM, Edwards C. Cushing's syndrome. *Clin Endocrinol Metab* 1972;1:451–490.
3. Kaminski HJ, Ruff RL. Neurologic complications of endocrine diseases. *Neurol Clin* 1989;7:489–508.
4. Whisnant Reiser L, Reiser MF. Endocrine disorders: Cushing's syndrome. In: Kaplan H, Sadock BJ, eds. *Comprehensive textbook of psychiatry*. Baltimore: Williams and Wilkins; 1985:1171–1172.
5. Dolan RJ, Friston KJ. Positron emission tomography in psychiatric and neuropsychiatric disorders. *Semin Neurol* 1989;9:330–337.
6. Muncke A. Glucocorticoid inhibition of glucose uptake by peripheral tissues: old and new evidence, molecular mechanism and action. *Perspect Biol Med* 1971;14:265–289.
7. Kadekaro M, Masanori I, Gross P. Local cerebral glucose utilization is increased in acutely adrenalectomized rats. *Neuroendocrinology* 1988;47:329–334.

8. De Souza B, Brunetti A, Fulham MJ, et al. Pituitary microadenomas: a PET study. Radiology 1990;177:39–44.
9. Kaye TB, Crapo L. The Cushing's syndrome: an update on diagnostic tests. Ann Intern Med 1990;112:433–444.
10. Gold EM. The Cushing syndromes: changing views of diagnosis and treatment. Ann Intern Med 1979;90:829–844.
11. Brooks RA, Friauf WS, Sank VJ, Cascio HE, Leighton SB, Di Chiro G. Initial evaluation of a high resolution positron emission tomograph. In: Greitz T, Ingvar DH, Widen L, eds. The metabolism of the human brain studied with positron emission tomography. New York: Raven Press; 1985:351–361.
12. Sokoloff L, Reivich M, Kennedy C, et al. The ^{14}C-deoxyglucose method for the measurement of local cerebral glucose utilization: theory procedure and normal values in the conscious and anesthetized albino rat. J Neurochem 1977;28:897–916.
13. Brooks RA. Alternative formula for glucose utilization using labeled deoxyglucose. J Nucl Med 1982;23:538–539.
14. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with [^{18}F]2-fluoro-2-deoxy-d-glucose: validation of method. Ann Neurol 1979;6:371–388.
15. Reivich M, Alavi A, Wolf AP. Glucose metabolic rate kinetic model parameter determination in man: the lumped constants and rate constants for [^{18}F]fluorodeoxy-glucose and [^{11}C]deoxyglucose. J Cereb Blood Flow Metab 1985;5:179–192.
16. Fulham MJ, Brunetti A, Aloj L, Raman R, Dwyer AJ, Di Chiro G. Decreased brain glucose metabolism in patients with brain tumors: an effect of corticosteroids. J Neurosurg 1995;83:657–664.
17. Cohen SM. Cushing's syndrome: a psychiatric study of 29 patients. Br J Psychol 1980;136:120–124.
18. Jeffcoate WJ, Silverstone JT, Edwards CRW, Besser GM. Psychiatric manifestations of Cushing's syndrome: response to lowering of plasma cortisol. QJ Med 1979;48:465–472.
19. Starkman MN, Scheingart SE. Neuropsychiatric manifestations of patients with Cushing's syndrome: relationship to cortisol and adrenocorticotropic hormone levels. Arch Intern Med 1981;141:215–219.
20. Hatazawa J, Brooks RA, Di Chiro G, Bacharach SL. Glucose utilization rate versus brain size in humans. Neurology 1987;37:583–588.
21. Evans RM, Arriza JL. A molecular framework for the actions of glucocorticoid hormones in the nervous system. Neuron 1989;2:1105–1111.
22. Horner HC, Packan DR, Sapolsky RM. Glucocorticoids inhibit glucose transport in cultured hippocampal neurons and glia. Neuroendocrinology 1990;52:57–64.
23. Packan DR, Sapolsky RM. Glucocorticoid endangerment of the hippocampus: tissue steroid and receptor specificity. Neuroendocrinology 1990;51:613–618.
24. Sapolsky RM, Uno H, Rebert CR, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 1990;10:2897–2902.
25. McEwen BS, de Kloet ER, Rostene W. Adrenal steroid receptors and actions in the nervous system. Phys Rev 1986;66:1121–1188.
26. Ahima RS, Harlan RE. Charting of Type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. Neuroscience 1990;39:579–604.
27. Olgemoller B, Schon J, Wieland O. Endothelial plasma membrane is a glucocorticoid regulated barrier for the uptake of glucose in to the cell. Mol Cell Endocrinol 1985;43:165.
28. Horner HC, Munck A, Lienhard GE. Dexamethasone causes translocation of glucose transporters from the plasma membrane to an intracellular site in human fibroblasts. J Biol Chem 1987;262:17696–17702.
29. Sokoloff L. Cerebral circulation, energy metabolism and protein synthesis: general characteristics and principles of measurement. In: Phelps ME, Mazziotta JC, Schelbert HR, eds. Positron emission tomography and autoradiography: principles and applications in the brain and heart. New York: Raven Press; 1986:1–71.
30. Momose KJ, Kjellber RN, Kliman B. High incidence of cortical atrophy of the cerebral and cerebellar hemispheres in Cushing's disease. Radiology 1971;99:341–348.
31. Bentson J, Reza M, Winter J, Wilson G. Steroids and apparent cerebral atrophy on computed tomography scans. J Comput Assist Tomogr 1978;2:16–23.
32. Okuno T, Ito M, Konishi Y, Yoshioka M, Nakano Y. Cerebral atrophy following ACTH therapy. J Comput Assist Tomogr 1980;4:20–23.
33. Baxter LR, Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989;46:243–250.
34. Silfverskiold P, Risberg J. Regional cerebral blood flow in depression and mania. Arch Gen Psychiatry 1989;46:253–259.
35. Uytenhoef P, Portelange P, Jacquy J, et al. Regional cerebral blood flow and lateralized hemispheric dysfunction in depression. Br J Psychiatry 1987;143:128–132.

Technetium-99m-ECD SPECT Fails to Show Focal Hyperemia of Acute Herpes Encephalitis

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This is a case of herpes simplex encephalitis (HSE) examined with ^{99m}Tc-ethyl cysteinate dimer (ECD) and ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT. Static images obtained with ^{99m}Tc-ECD showed a reduced tracer uptake of the temporal lobe but focal hyperactivity using ^{99m}Tc-HMPAO. Dynamic images indicated regional increase of cerebral blood perfusion with both tracers. Technetium-99m-ECD had rapid washout from the inflammed tissue, while ^{99m}Tc-HMPAO had avid uptake. Hypofixation of ^{99m}Tc-ECD leads to failure to detect the characteristic finding of temporal lobe hyperemia in acute HSE.

Key Words: herpes simplex encephalitis; technetium-99m-ethyl cysteinate dimer; technetium-99m-hexamethyl propyleneamine oxime; tracer uptake; SPECT

J Nucl Med 1998; 39:790–792

Technetium-99m-ethyl cysteinate dimer (^{99m}Tc-ECD) has been proposed as a safe and effective marker of regional cerebral perfusion. In normal controls and patients with chronic neurologic disorders, the distribution of ECD was shown to be linearly related to regional cerebral blood flow as measured by SPECT with ^{133}Xe with only mild underestimation of flow at the high end of the normal range (1). In comparison to ^{99m}Tc-hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO), the distribution of both tracers appeared initially to be similar with the advantage that ^{99m}Tc-ECD had greater radiochemical stability and more rapid washout from extracerebral tissues (2,3). Subsequently, it is reported that ^{99m}Tc-ECD does not show reperfusion hyperemia in the subacute phase of a stroke (4,5). We present a case in which ^{99m}Tc-ECD fails to show hyperemia associated with focal cerebral inflammation. Focal hyperactivity of the temporal lobe has been considered a hallmark finding of acute herpes simplex encephalitis (HSE) on static brain SPECT (6–9) using ^{99m}Tc-HMPAO.

CASE REPORT

A 73-yr-old woman with a headache and subfebrile temperature had become confused over the course of a few days. Neurologic findings consisted of short episodes of aphasia and a mild right hemiparesis. There was a past history of two ischemic strokes, and CT of the head showed leukoaraiosis with old lacunar lesions of the basal ganglia bilaterally. A diagnosis of cerebrovascular disease aggravated by some infectious process was considered. Further deterioration with psychotic symptoms and somnolence prompted