Brain Basal Metabolism and Flow Reserve Predict Therapeutic Response in Most Cognitively Impaired Patients

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Abstract

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Title: Brain basal metabolism and flow reserve predict therapeutic response in most cognitively impaired patients

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Background:
Patterns of basal brain metabolism and flow reserve, determined by comparing basal and stimulated perfusion, are widely described to correlate with various causes of cognitive impairment; however, there are few descriptions correlating these patterns with patient's therapeutic responses.

Methods:
SPECT scanning used a dual-head gamma camera with 5.5 mm resolution. Patients received 20 mCi Tc-99m-HMPAO for stimulated or basal perfusion (also a surrogate for basal metabolism) or 10 mCi F-18-FDG or 20 mCi Tc-99m-ECD for basal metabolism, injected in a quiet, dark room. Perfusion stimulants were acetazolamide 500 mg IV, nitroglycerin 0.6+-0.2 mg sublingual, omega 3 unsaturated acid ethyl esters (Lovaza^{R}) 10 gram oral, or Mona Vie^{R} (acai fruit juice) 100 ml oral. Cerebral Perfusion and Metabolic indices (CMi, CPi) for each patient, including 20 with low likelihood of disease, were calculated from the SPECT images. Patients were studied in the course of neurologic and neuroendocrine practice after complaints of cognitive impairment. Therapies included acetyl-cholinesterase inhibitors, Namenda^{R}, Lovaza^{R}, nonbranded fish oils, antihypertensives, statins and amantadine (for traumatic brain injury).

Results:
Brain SPECT defined three patterns: 1) CMi + (5+-2)% = CPi (normal if 49%< CMi < 71%) ; 2) CMi +(5+-2)% < CPi; 3) CMi + (5+-2)% > CPi. Therapeutic responses in 6 to 18 months among 20+-5 patients in each group were best (60% improved) for group 3, intermediate (30% improved) for group 2 and worst (< 10% improved) for group 1. Diagnoses included multiple causes of mild cognitive impairment in 80% and dementia in 20%. Over 70% of dementias were mixed, predominant types: vascular in 40%, Alzheimer's in 30%, probable Lewy body in 15%, fronto-temporal in 5%, traumatic brain injury in 5% and miscellaneous in 5%.

Conclusions:
Stimulated perfusion is normally slightly increased over basal metabolism as defined by brain SPECT. Patients with decreased cerebral flow reserve (perfusion deficits) respond more readily to widely available therapy than those with predominant metabolic deficits and more intact flow reserve which characterize early neurodegenerative diseases. Patients with similar, fixed deficits in perfusion and metabolism (nonresponsive to perfusion stimulants) include advanced neurodegenerative and vascular dementias which have the worst prognosis.

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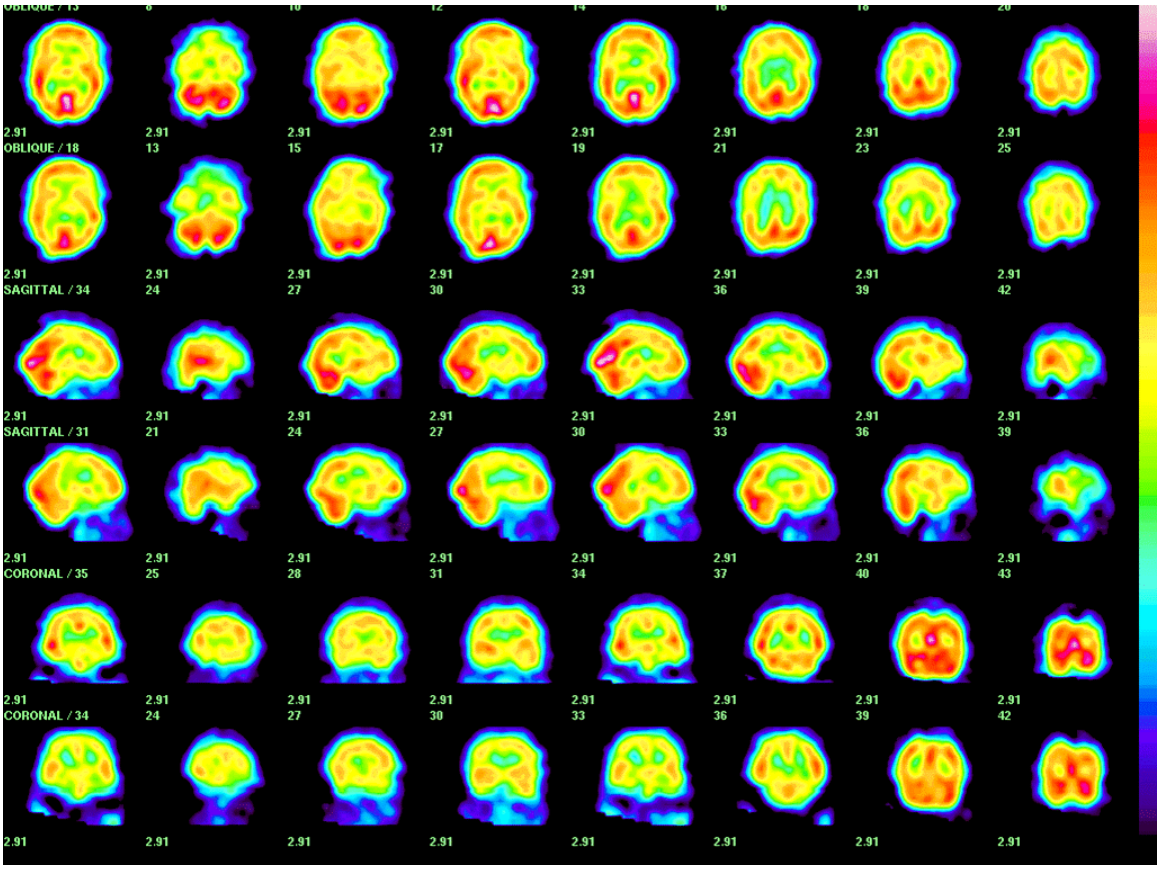
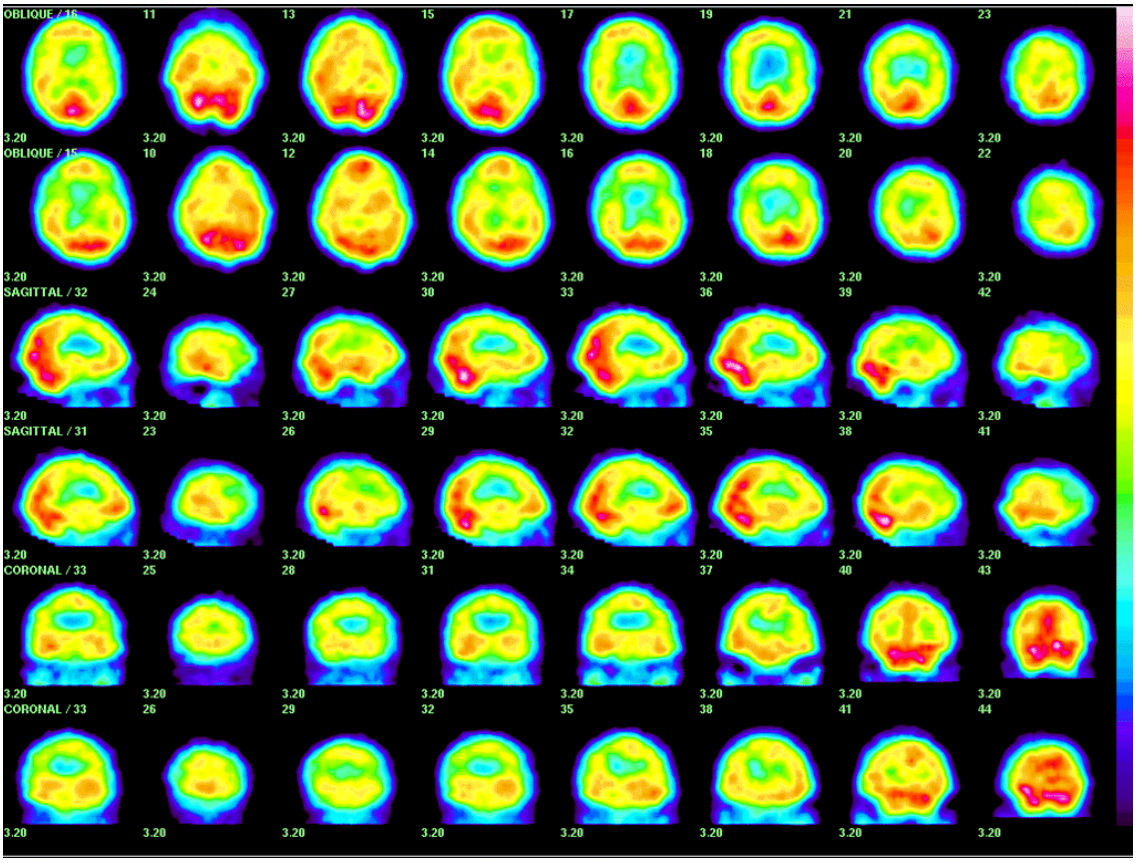
Basal (bottom of each set of three images) and IV acetazolamide-stimulated (top of each set of three images) brain SPECT: 54 year-old type 2 (noninsulin dependent) diabetic woman, well-controlled hypertensive on angiotensin converting enzyme inhibitor, fosinopril, treated for depression with sertraline. Tracer distribution is normal, apart from minor left orbitofrontal deficit (saggital image 33) and borderline low cerebrovascular flow reserve: Cortical Metabolic index 62.9% and Cortical Perfusion index 62.3%.



Dorsolateral frontal and wedge-shaped right parietal decreased basal (bottom each of 3 rows) Tc-99m-HMPAO distribution with low CMi 35% and near normal CPi 51%, consistent with anterior cerebral artery disease and insulin-dependent diabetic aging in an 82 year-old hypertensive, hyperlipidemic man post CABG, with peripheral vascular, renal, prostate disease, COPD and DJD, with dysgeusia due to stroke 4 years earlier. Pattern 2 here associated with grave prognosis: neoplasia-related cardiovascular death in two weeks.


OBLIQUE / 16
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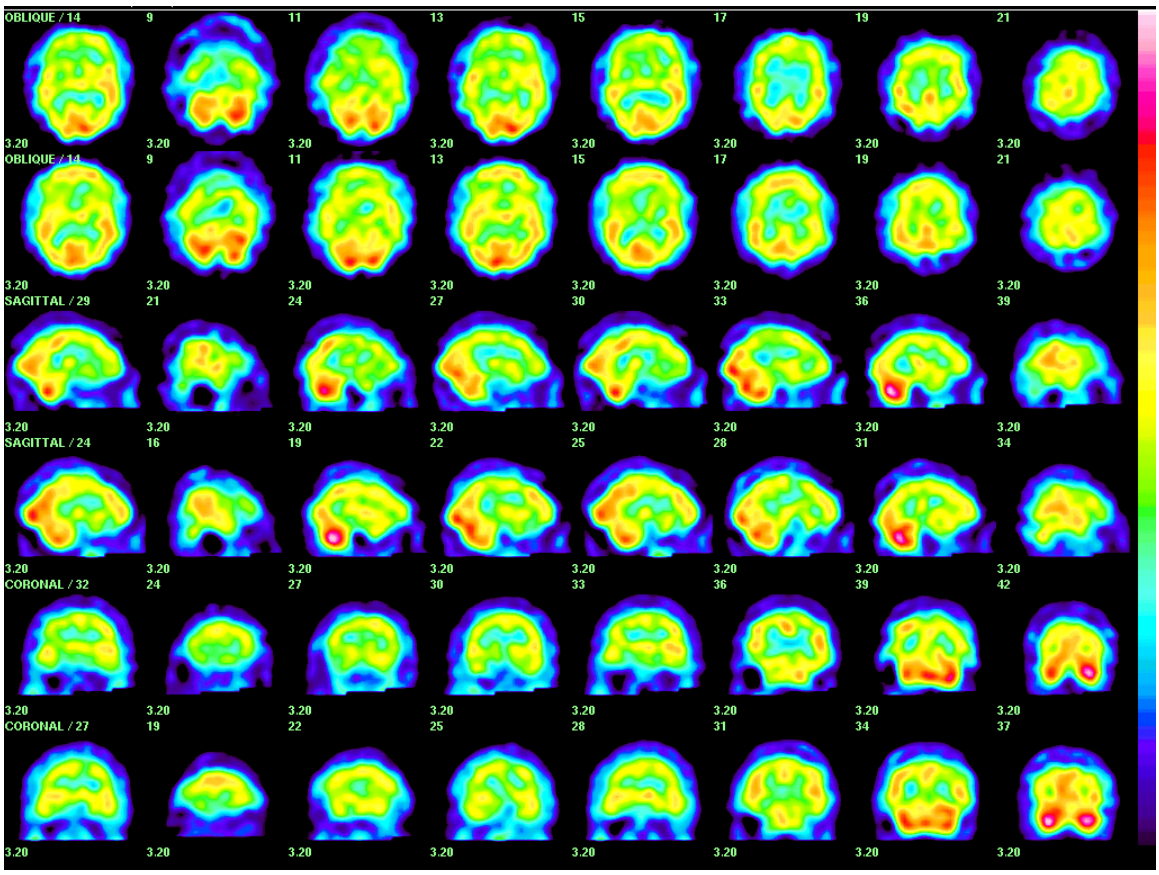
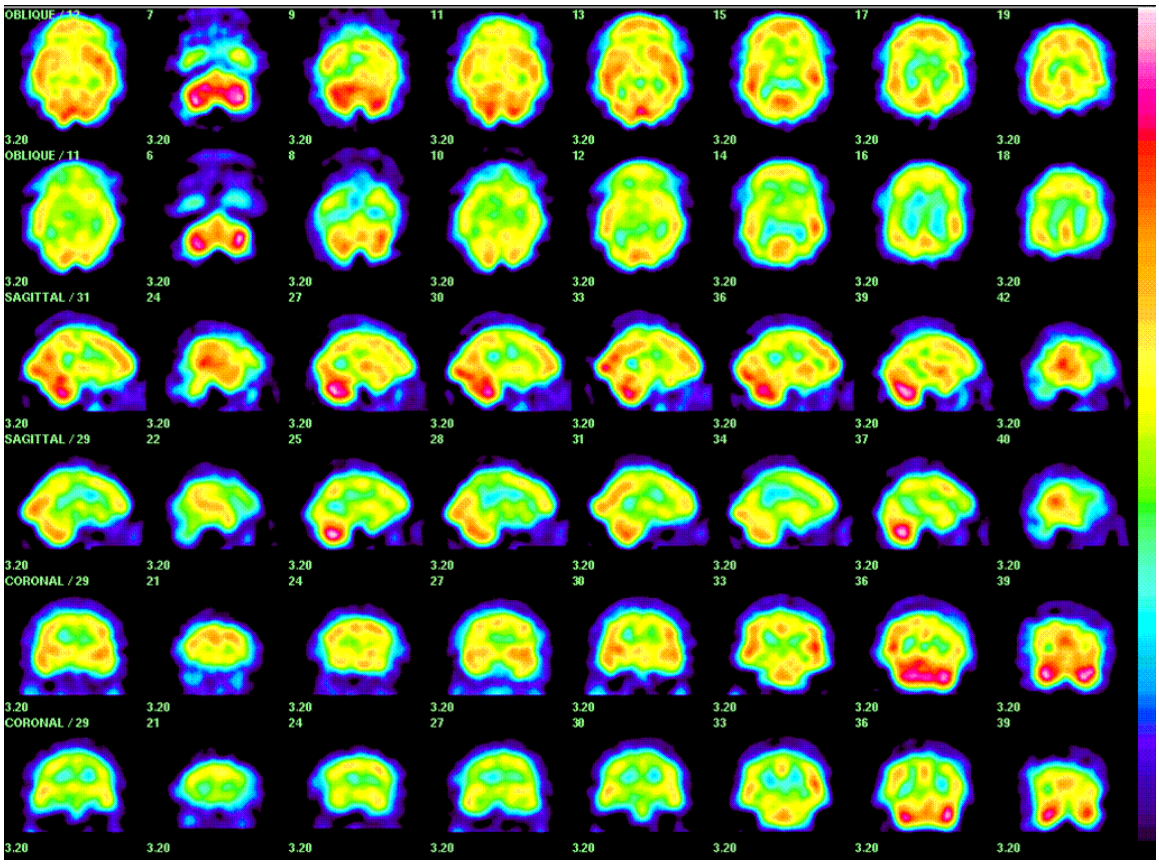
A 29 year-old diabetic (NIDDM), hyperlipidemic, hypertensive and polycystic ovarian bipolar nurse with memory loss: Initial CMi 46.39% and CPi 44.05% (pattern 1) is shown to the right, with omega-3 unsaturated fat stimulated Tc-99m-HMPAO Brain SPECT (top of each of 3 paired rows opposite, basal images on bottom). Note bilateral temporal and orbitofrontal abnormality, exacertabed (eg. saggital 24) or unimproved by perfusion stimulus.



After Lovaza 4 g oral daily for 11 months CMi 40.91% decreased and Diamox stimulated CPi 54.5% increased and cognitive complaints including confusion and memory loss stabilized (MMSE 28/30). Note more normal perfusion-stimulated images on top of each of 3 paired rows of images, as compared either to the new basal images (bottom of each of 3 paired rows to the right) or the initial perfusion images (top of each of 3 paired rows above to the right).



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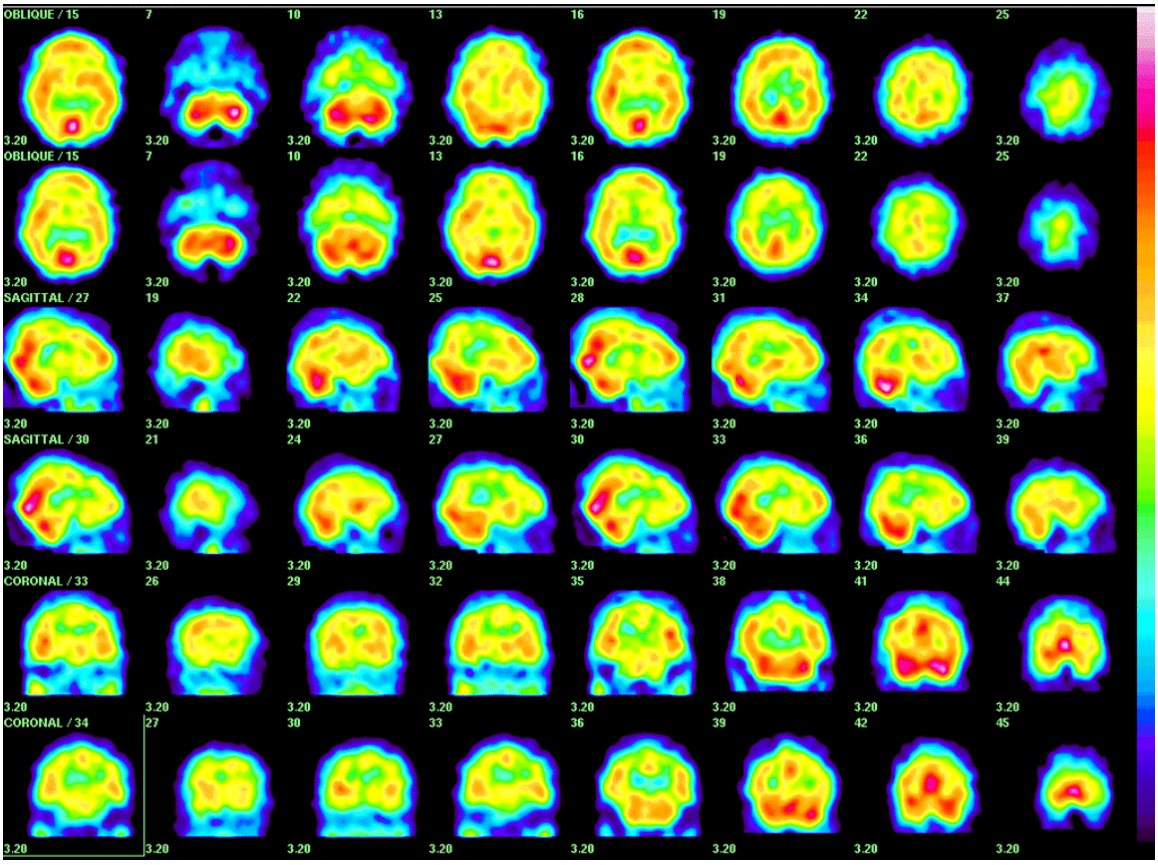
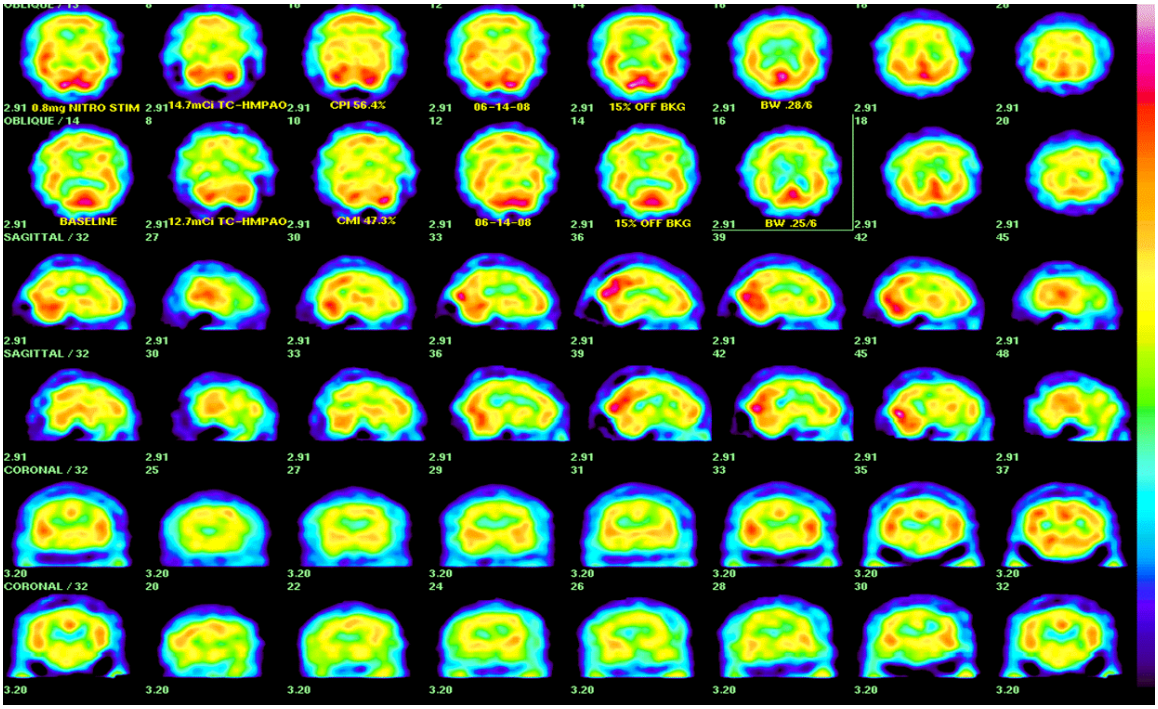
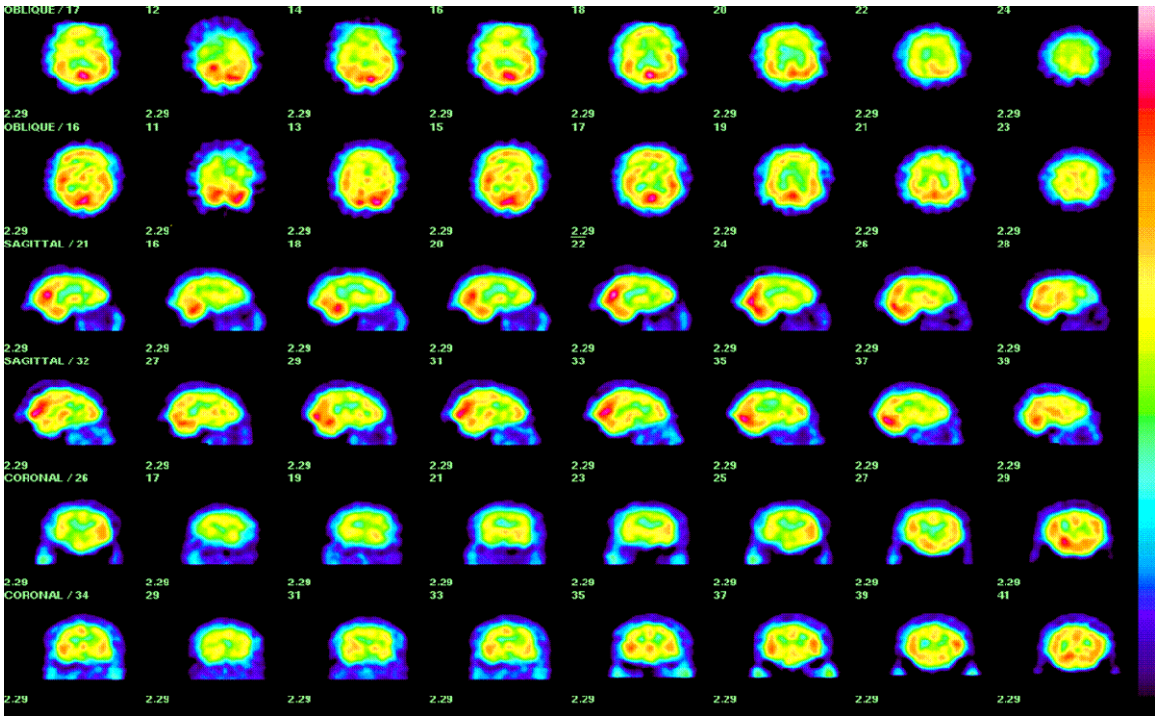
A 56 year-old hypertensive, hyperlipidemic, woman with TIA (syncope and subsequent short-term memory loss) and autoimmune thyroiditis (euthyroid on l-thyroxine) had initial Brain SPECT pattern 2: CMi 42.0%, CPi 50.9%. Shown to the right is improved Tc-99m-HMPAO Brain SPECT 10 months later with CMi 53.5%, CPi 53.4%. Conversion to pattern 1 suggests potential for further improvement which was observed on clopidogrel, ramipril, rosuvastatin and omega-3 fish oil, 4 grams daily over 16 months.



49 year-old recalcitrant and uncontrolled (usual HgbA1c > 11%) type 2 diabetic (IDDM) with pattern 3: CMi 48%, CPi 54%, shown to the right upper set of images, experienced a downhill clinical course with repeated falls, confusion, continued severe hyperglycemia, stage 2 hypertension, and after 2 years had CMi 39%, CPi 44% with more prominently decreased basal tracer distribution, posterior and orbitofrontal bilaterally, periventricular and cerebellar, consistent with non-specific neurodegeneration, metabolic encephalopahaty, and unipolar depression.





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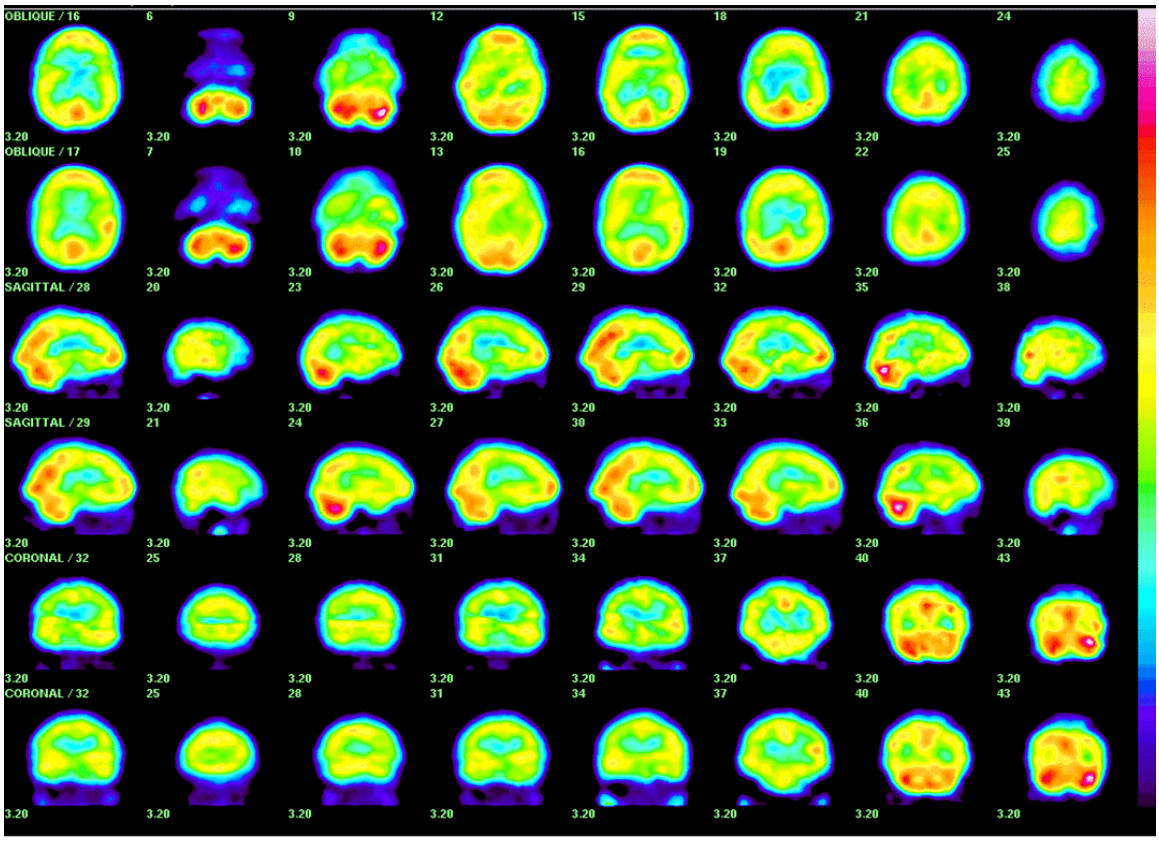
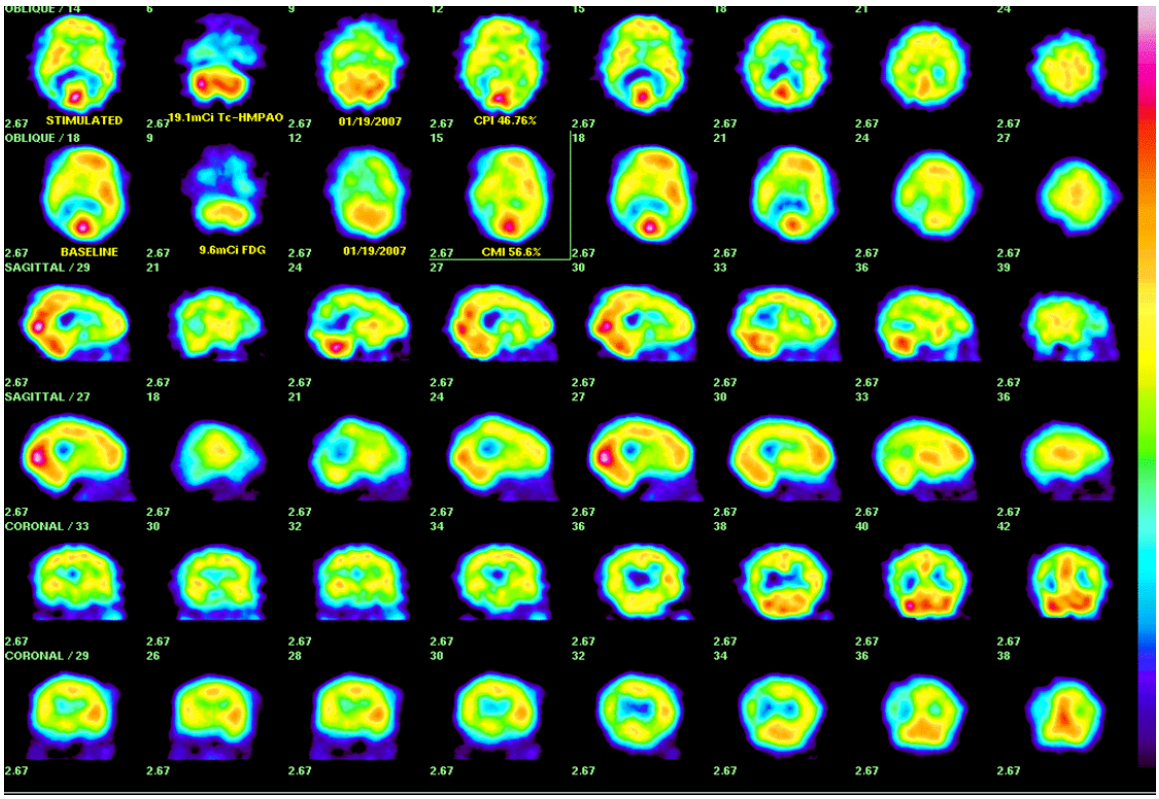
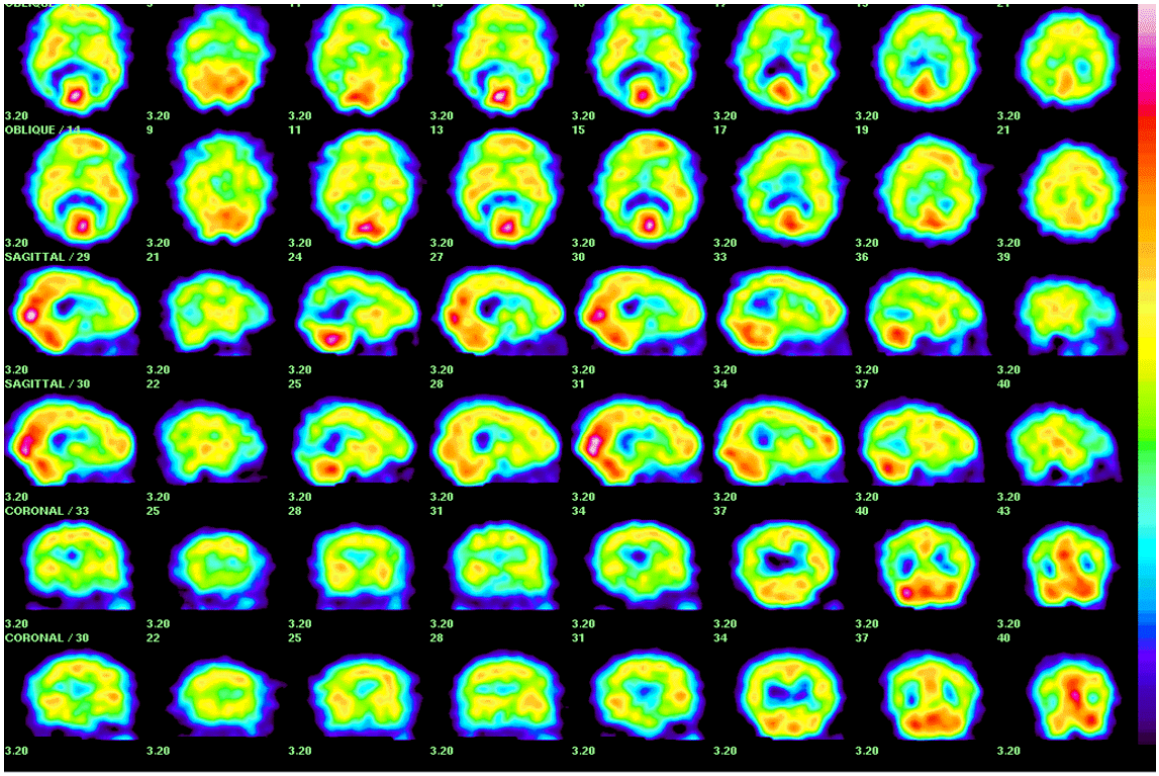
Pattern 1: CMi 47%, CPi 37% to the right, used 0.8 mg nitroglycerin sublingual (top of each of 3 paired image rows). Note left temporal deficit and parietal perfusion reserve deficit in a 53 year-old insulin resistant, hyperlipidemic dietician with unmeasurably low DHEA sulfate who took estrogens for 30 years before experiencing sudden vertigo after an airline flight. Therapy was cessation of estrogen, Plavix 75 mg daily, and omega-3 unsaturated fish oil 6 grams oral daily and rosuvastatin 10 mg each evening. Replacement DHEA was not tolerated.



Memory loss in a 53 year-old hyperlipidemic, depressed IRS employee who had initial pattern 1: CMi 40%, CPi 35%, his Tc-99m-HMPAO basal and omega 3 unsaturated fat stimulated (stimulated top of each of 3 paired image rows to right) is consistent with mixed vascular-Alzheimer's dementia. After 6 months therapy including Aricept (later Exelon), Namenda, Lovaza, Zocor, Aggrenox (later Plavix), folic acid, Pletal, Lexapro and lithium, patient continued working with CMi improved to 50% (borderline low), CPi 46%. There was little clinical change and neuropsychological testing showed IQ 83, decreased compared to estimated premorbid IQ 120. This patient raises question of whether there is a threshold level of hypoperfusion, near 35% noted in this patient, below which available perfusion stimulants are still unlikely to result in significant improvement in either imaging parameters or clinical function. Abnormal urine porphyrins recently obtained raised the question of possible mercury exposure and potential chelation therapy with 2,3-dimercapto-1-propane sulfonic acid (DMPS).


STIMULATED
19.1mCi Tc-HMPAO
01/19/2007
CPI 46.76%
OBLIQUE / 18
BASELINE
9.6mCi FDG
01/19/2007
CMI 56.6%
SAGITTAL / 29
SAGITTAL / 27
CORONAL / 33
CORONAL / 29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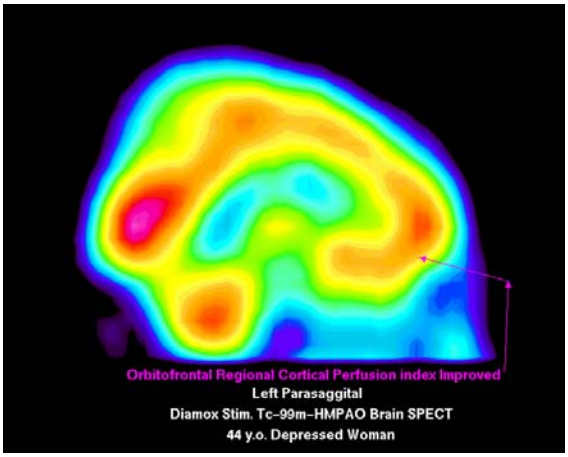
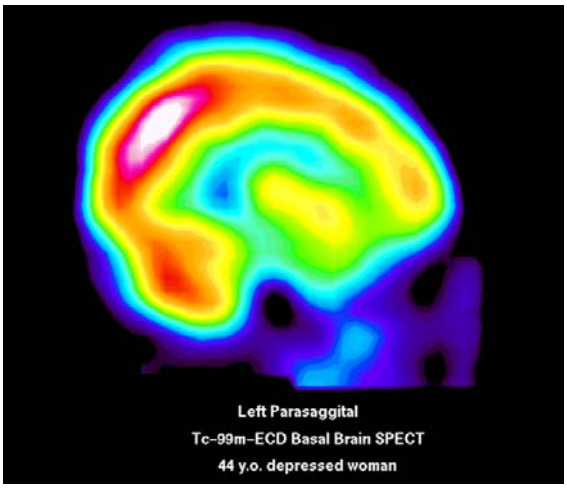
CORONAL / 33
CORONAL / 30

5

43 year-old depressed woman with Graves' hyperthyroidism and ophthalmopathy demonstrates regional orbitofrontal deficit in the basal study, below, and to the right, effect of perfusion stimulation with acetazolamide, which results in improvement to the extent of its near normalization. The patient complained of "brain fog", a frequent complaint in patients with Hashimoto's encephalopathy, which we and others have previously described in Graves' disease as well.



We have also described (American Association of Clinical Endocrinology National Meeting, 2008) a pseudo-Alzheimer's pattern of bilateral parieto-occipital and mesial temporal hypometabolism with preserved perfusion reserve to multiple perfusion stimulants, including the juice of the acai berry (MonaVie). This patient improved clinically with thionamide therapy and Bystolic, which may stimulate cerebral perfusion more than other beta blockers, suitable in this instance but not for migraine.



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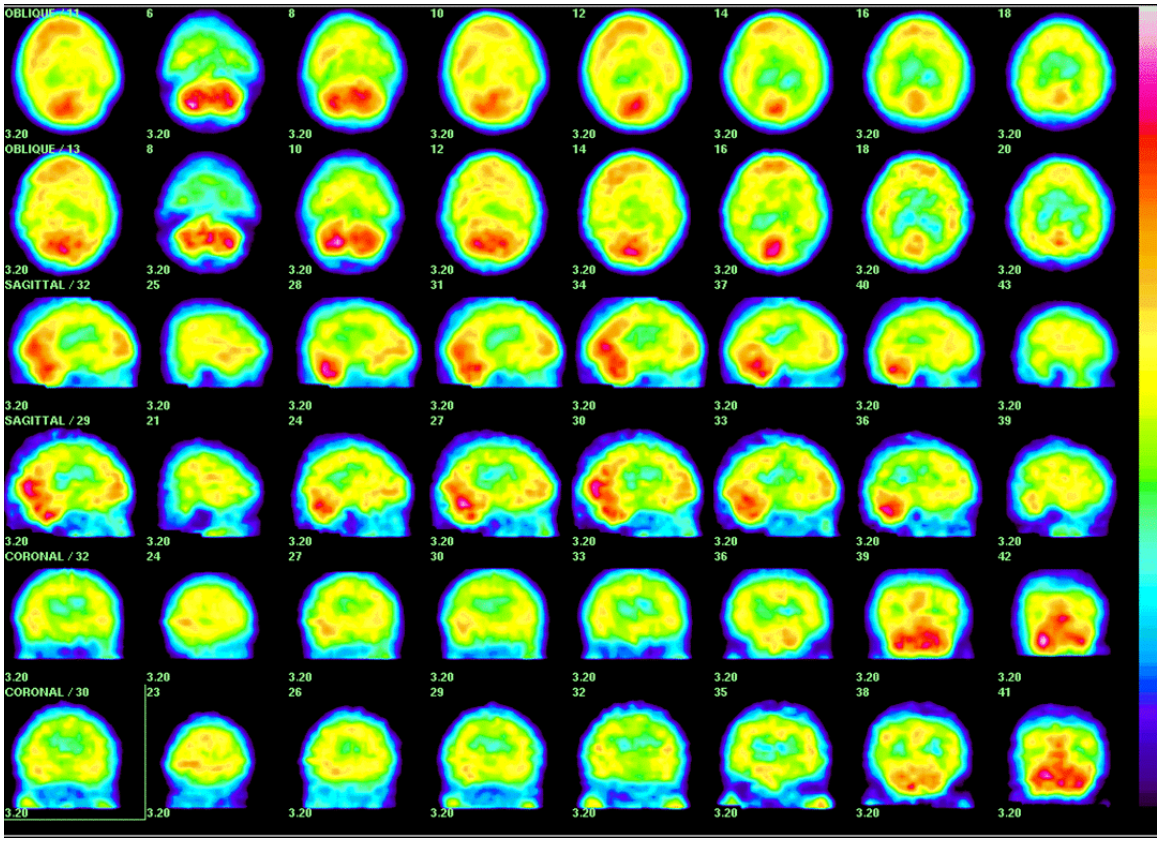
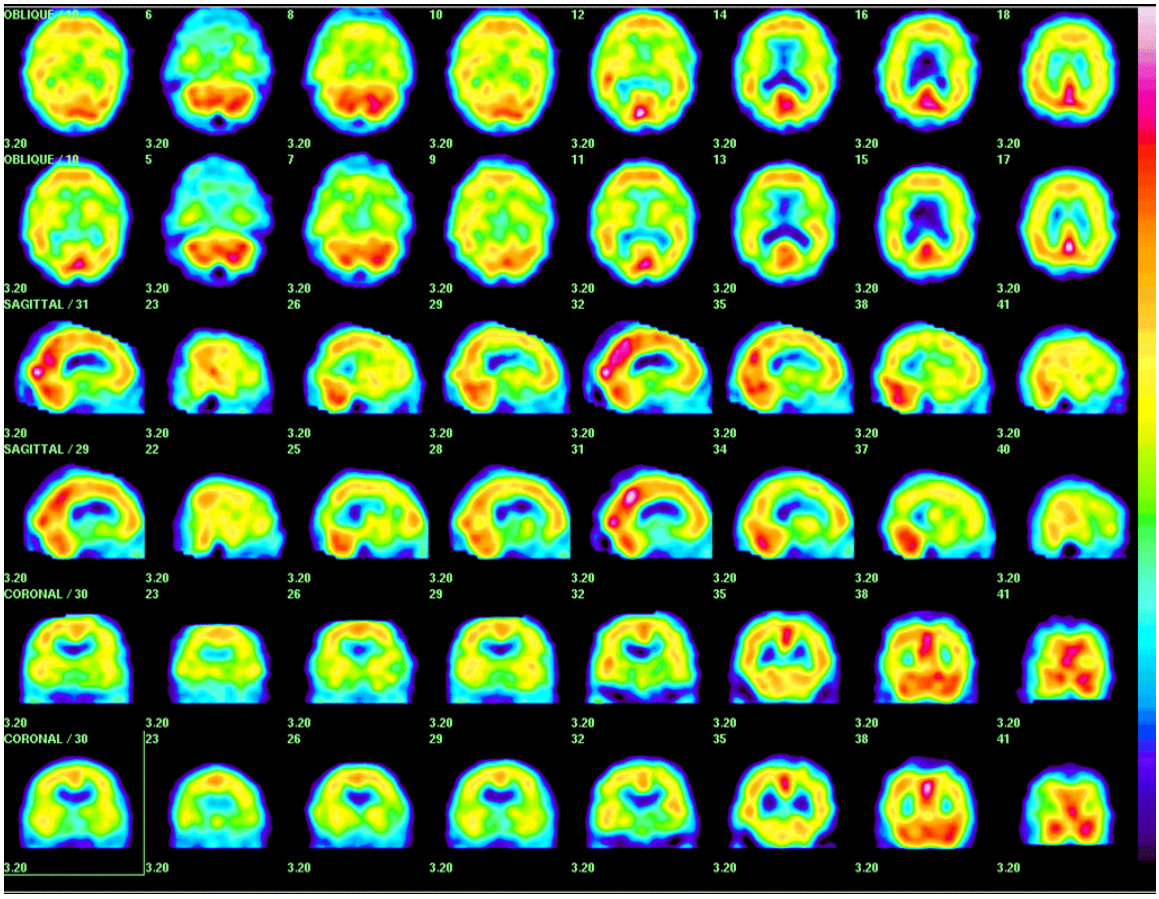
Pattern 2: CMi 40%, CPi 48% in a 34 year-old man with confusion, headaches and memory loss post concussion due to severe closed head trauma. Nitroglycerin-stimulated Tc-99m-HMPAO brain SPECT is shown to the right (top of 3 paired image rows) over basal images. The patient was not prescribed amantadine and did not improve clinically.



Early Alzheimer's disease or Mild Cognitive Impairment (MCI) in a 70 year-old man with memory loss and CMi 49%, CPi 48% (pattern 1), the abnormalities demonstrated better by parieto-occipital and temporal regional CMi 33% and 34%. Therapy of MCI is presently approved by U.S. FDA for one natural product: Cerefolin NAC, although our experience has been principally with omega-3 unsaturated marine oil (Lovaza), renin-angiotensin-system inhibitors (eg. angiotensin converting enzyme inhibitors) and other agents cerebral perfusion stimulants.



Summary

Experience with Brain SPECT comparing basal metabolic and stimulated perfusion images over a ten year period shows that patients with normal cerebral perfusion reserve, amounting to an approximately 5% increase of CPi over CMi actually fare the worst with available therapies. Remarkably, those with deficits in CPi relative to CMi (including those with nearly equal CMi and CPi) do the best with available therapeutic agents, which arguably may be primarily directed toward improvement in cerebral hypoperfusion (cf. in trials of most Alzheimer's agents the vascular or mixed dementia patients did at least as well if not better than the neurodegenerative patients). As we have previously reported, the frequency of mixed patterns of dementia is much greater in everyday clinical practice than classical dementia of the Alzheimer type. Further mechanisms of cerebral injury with potential for evolving therapy include toxic metal exposure (eg. mercury, lead, aluminum), neurosteroid and other neuroendocrine metabolic abnormalities, both genetic and acquired. Future therapeutic initiatives will continue to benefit from neurobiomarkers such as brain SPECT, which in our experience correlates well with both clinical status and prognosis.