

Cerebrovascular Reserve, Dementia Risk and Renal Function

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Abstract

Background: Relationships among dementia risk factors are well established: diabetes and related complications, nephropathy and retinopathy, coexist with hypertension, obesity and coronary disease. Increasing evidence implicates brain hypoperfusion as an early and potentially treatable aspect of dementia risk. In this context, the relation of renal dysfunction to cerebrovascular reserve is pertinent in vascular risk subgroups, as well as brain trauma and metal toxicity.

Methods: Outpatients (60% women, 40% men; 65% Caucasian; ages 25-91 years, average 55±10 years,) with cerebral ischemia or related symptoms (eg. TIA, cognitive impairment, post concussion, complex migraine) were injected with radiolabelled tracers, followed brain SPECT. Cortical metabolic and perfusion indices (CMi, CPi) for basal and perfusion-stimulated SPECT were scaled similarly to rest and stress ventricular ejection fractions: normal CMi 50-72%, normal CPi 53-75% and normal cerebrovascular reserve (CR) if $CPi > (CMi+3)\%$. Quantitative urine porphyrins screened for metal toxicity. Renal function was calculated by MRDD. Patients with type 2 diabetes were treated to average HbA1c 8%; blood pressures were treated to < 140/90 mm Hg.

Results: CR was abnormal in 64% (51/80) of hypertensives, 61% (54/89) of diabetics, 64% (32/50) of insulin resistant nondiabetics, 57% (16/28) of mild brain trauma patients and 58% (42/78) of metal toxic patients. CR was abnormal in 50% (1/2) of patients with GFR < 15 ml/min; but normal in 90% (18/20) of patients with GFR 15 to 60 ml/min. In each risk group, mean age did not differ between patients with normal versus abnormal CR.

Conclusions: Abnormal CR is a fundamental aspect of disorders predisposing to dementia, including diabetes, hypertension, insulin resistance, metal toxicity and brain trauma. Renal dysfunction unexpectedly correlates inversely with abnormal CR, possibly because of an artifact (eg. a greater perfusion-stimulated cerebral arterial input function, if uncorrected for renal failure). Hence, high prevalence of abnormal CR typical of dementia may be underestimated, particularly in conditions associated with renal failure, such as metal toxicity, diabetes and hypertension.

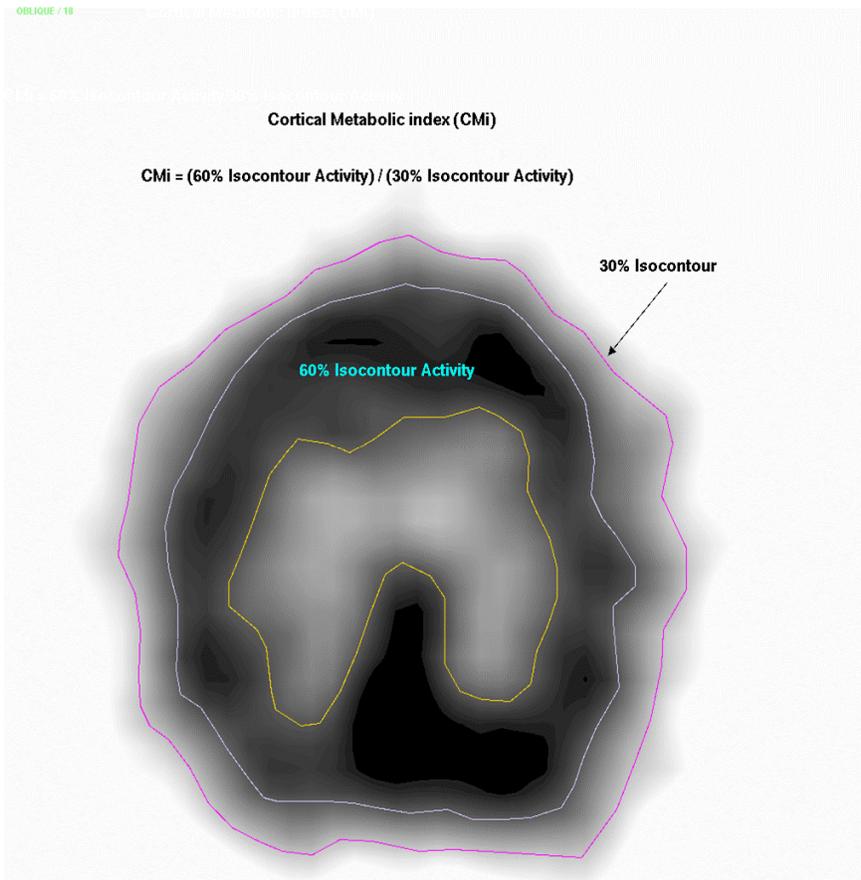


Fig. 1 (Above, Left): Axial SPECT slices are defined parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of the normal-sized lateral ventricles. Activity display uses a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Computer-selected isocontours define areas that contain activity above a certain fraction of the peak activity. The 30% isocontour represents total brain activity in that axial slice, chosen slightly outside the actual external edge of the brain (usually near a 60% isocontour) to correct for attenuation. The 60% isocontour represents the edge of normally functioning neurons, and the Cortical Metabolic index (CMi), calculated as the ratio of activity within the 60% to that within the 30% isocontours, is a measure of the fraction of brain function due to normal neuronal function. The Cortical Perfusion index (CPi) is similarly calculated from 60% and 30% isocontours after the patient has received a cerebral perfusion stimulant such as 0.5 to 1 g acetazolamide IV or 0.4 to 0.8 mg nitroglycerin sublingual.

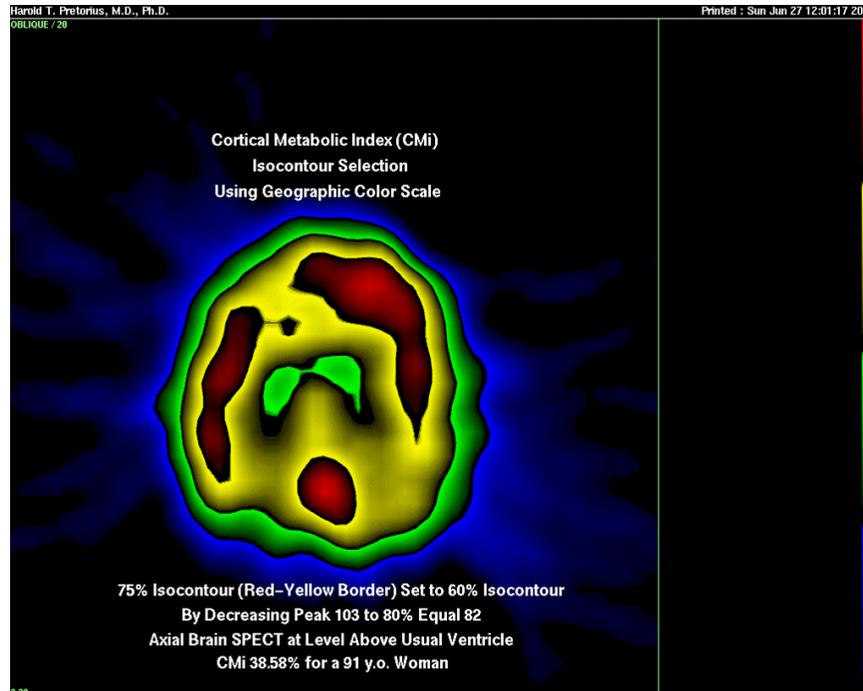


Fig. 2 (Above, Right): The Cortical Metabolic index (CMi) 38.58%, for a 91 year-old moderately demented woman is demonstrated using a color scale, available on nearly all commercial SPECT instruments. In patients with low likelihood of disease the values for Cortical Metabolic index (performed with patients injected with metabolic or basal blood flow tracers such as Tc-99m-HMPAO, Tc-99m-ECD or F-18-FDG) are 50 to 72% and for CPi increase to 53 to 75%. The Cerebral Flow Reserve index CR is simply CPi minus CMi, which is normally (defined in low likelihood disease patients) a positive number > 3%. We found previously that abnormal CR values < 3% or even negative numbers, are typical of cerebrovascular or associated disease such as diabetics, prediabetics, oxidative metal exposed and traumatic brain injured.

1. Summary

Dementia is a clinical syndrome whose etiology is multifactorial. Multiple interrelated dementia risk factors coexist but may not have equal or simply additive pathophysiologic effects nor equal influence on quantitative biomarkers of dementia. Among the dementia risk factors, including cerebrovascular disease, hypertension, diabetic or nondiabetic insulin resistance (which tend to coexist with obesity), and even traumatic brain injury and neurotoxic metal exposure, there is a common denominator of cerebral hypoperfusion. Brain SPECT, particularly using protocols that compare basal metabolism and stimulated perfusion, is well suited to detect cerebral hypoperfusion. We focused not only on absolute measures but also the cerebral vascular reserve (CR), defined as the difference of Cortical Perfusion and Metabolic indices (CPi minus CMi). Renal dysfunction is of increasing interest as a dementia risk factor, particularly in light of its well recognized pathophysiologic interactions with hypertension, insulin resistance, and metal toxicity. We found that patients with even mild renal dysfunction had a remarkable tendency to preserved (CR) measured by brain SPECT. This effect

depended on total renal function and was not observed in patients with only unilateral renal dysfunction. Patients with bilateral renal dysfunction, despite usually normal CR, had a high risk of stroke and compromised cognitive function. Moreover, following significant stroke, brain SPECT measure of CR typically reverts to abnormal, even in the presence of continued renal dysfunction.

Although treatment results remain preliminary, the initial impression is that agents which relieve cerebral hypoperfusion have positive effects. These include antihypertensives, vasodilators such as nitrates and possibly cilostazol (recently recognized as effective stroke prevention in diabetics) and omega-3 unsaturated marine oil. An additional observation in this work was that either acute or chronic disruption of glycemic control contributes to cerebral hypoperfusion. Moreover, in both diabetics and nondiabetics, agents with positive modulation of glucose metabolism and possibly other neuroendocrine effects on body weight, including incretins, also have both acute and chronic effects on regional and global cerebral perfusion.

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2. Table 1. A demographic summary of the patients

Descriptive Information	Overall (n = 406)
Sex / Age	
Female / Male (ratio)	243 / 162 (1.50)
Mean Age in Years ± Std (range)	54.9± 15.9 (19 – 97)
Race	
Caucasian 76.0% Others* 24.0%	
Cerebral Flow Reserve index	
In renal patients	CPI.- CMi nml = (5+-2) 26.0% (19/73) Abnormal Decreased
21.9% had prior stroke	16/73 prior strokes Normal
Nml renal function 63.6% Abnormal CR (211/332)	Abnormal Decreased
With cerebral ischemia symptoms	
Urinary Porphyrins (µg/L)²	
Uroporphyrin (0 – 20)	14.6 ± 9.0
Heptacarboxyporphyrin (0 – 2)	5.0 ± 3.9
Hexacarboxyporphyrin (0 – 1)	0.8 ± 0.7

Pentacarboxyporphyrin (0 – 2)	1.5 ± 1.4
Coproporphyrin I (0-15)	24.0 ± 20
Corproporphyrin III (0-49)	55.6 +- 30
SPECT Scan Indices (%) ³	
CMI (50 – 72)	51.9 ± 8.0
CPI (53 – 75)	52 ± 8.0

* Black, Asian, Hispanic, or Mixed Ancestry.

² Mean ± standard deviation. Urinary porphyrins were measured by LabCorp (CLIA-certified) blinded as to the diagnosis/clinical severity of the subjects.

³ Mean ± standard deviation. SPECT scan indices were calculated blinded to LabCorp urinary porphyrin results.

Uroporphyrin = uP, Heptacarboxyporphyrin = (7cP), Hexacarboxyporphyrin (6cP), Pentacarboxyporphyrin (5cP), Coproporphyrin I + III = (total cP), Std = standard deviation

Urine porphyrin results are for the entire group of patients, and are somewhat biased by inclusion of patients eventually shown to have metal poisoning, who had marked elevation of coproporphyrin I and corproporphyrin III. Prior work from our group indicates a significant relation ($p < 0.004$) between increased corproporphyrin levels and decreased Cortical Perfusion index (CPI) for nondiabetics. We did not systematically investigate the relation of CPI or CR to porphyrin excretion in patients with renal dysfunction, although 8.2% (6/73) of total SPECT scans in patients with renal dysfunction had abnormal porphyrins. This is approximately half of the 15% of patients in our practice with cognitive complaints who have abnormal porphyrins and normal renal function.

3.

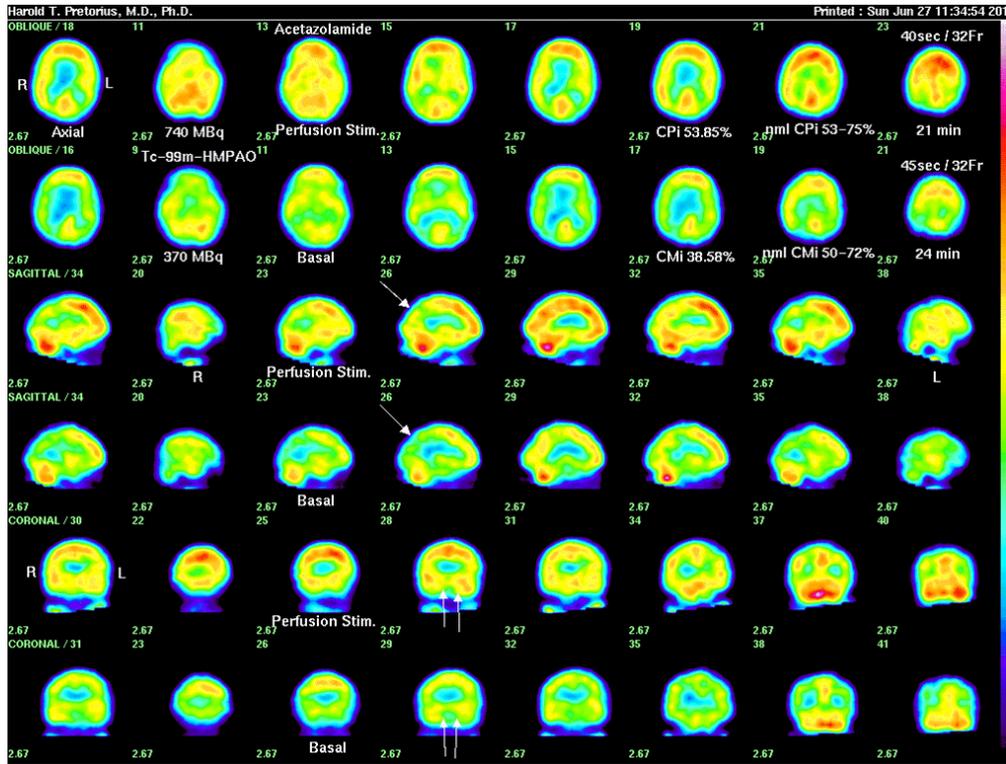


Fig: 3a: A 91 year-old woman has trouble finding the office and says she does not remember why she came. Her Test Your Memory (TYM) score is 30 of 50, consistent with moderately severe dementia, and her GFR is 55.3 ml/min, consistent with mild renal insufficiency. Brain SPECT, to the right, shows acetazolamide-stimulated perfusion (top of each of 3 rows of paired images) over basal (bottom of each of 3 rows of paired images), using the perfusion tracer: technetium-99m-hydroxy-methy-propyl-ene-amine (Tc-99m-HMPAO). The cerebral flow reserve (CR) is the Cortical Perfusion index (CPI) minus the Cortical Metabolic index (CMi), here (53.85 minus 38.58)% >> 3%, hence well within expected normal limits. A total of 73 SPECT scans in 64 patients with cognitive complaints and mild renal failure had average CMi (48.69+-9.39)%, average CPI (53.67+-10.3)% and average CR (5.04+-7.35)%. Only 19 scans in this group had abnormal CR and among these 57.9% (11/19) had strokes, 31.6% (6/19) had abnormal porphyrins and 15.8% (3/19) had active pituitary disease, at least one of these factors expected to decrease CR accounting for 14/19 cases with low CR and decreased renal function, so that 91.5% (54/59) of scans among patients with renal dysfunction and without overt cause for low CR had normal CR. The burden of disease in the renal failure group overall was high, with 21.9% strokes (16/73), 20.5% (15/73) congestive heart failure, 4.1% (3/73) severe renal failure on hemodialysis, and 1.4% (1/73) mortality in 2 years average follow-up.

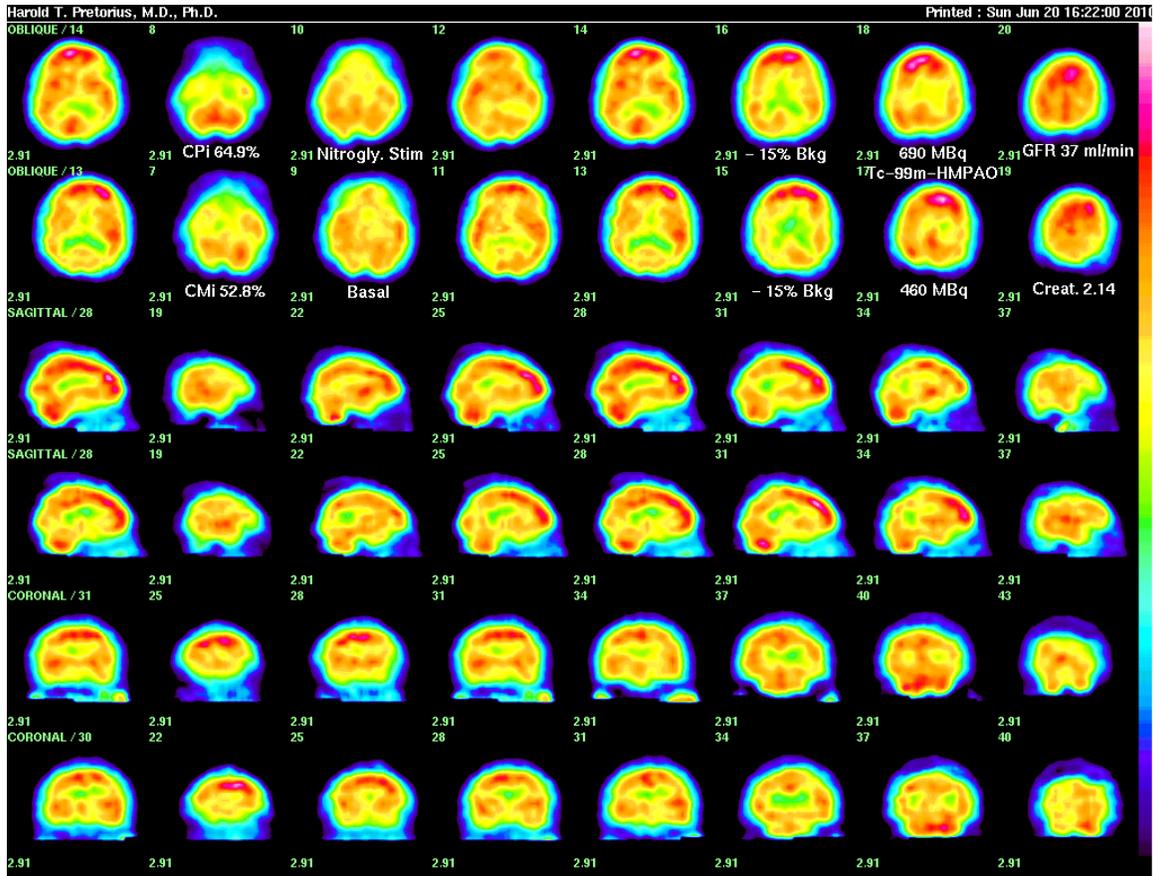


Fig 3b: Brain SPECT on the right with 0.8 mg nitroglycerin sublingual used for perfusion-stimulated images (top row of each of 3 paired rows of images; basal images are shown on the bottom row of each of the 3 paired rows) in a 75 year-old hypertensive African American man with relatively stable renal failure. Serum creatinine over the last 2 years was 1.60 to 2.25 mg/dl, and near the time of imaging, 2.14 mg/dl, corresponding to GFR 35 to 45 ml/min. The patient has Mild Cognitive Impairment but normal cerebral flow reserve (CR), here (64.9 minus 52.8)% \gg 3%. Among 81 hypertensive patient scans in 74 patients, average age (57.3+ 14.3) years, without renal dysfunction, only 27.2% (22/81) had normal CR.

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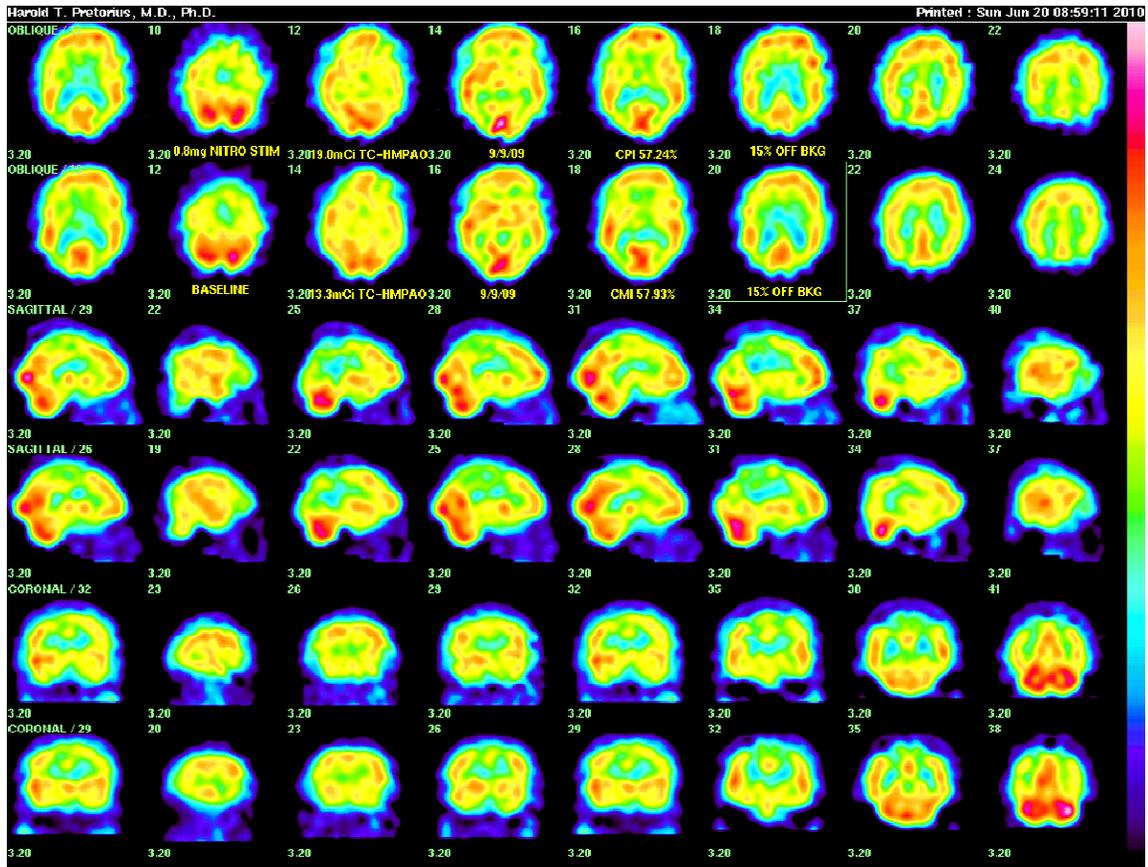


Fig. 4a: 48 year-old hypertensive type 1 (insulin dependant) diabetic man with mild cognitive impairment (TYM 42/50 similar to MMSE 27/30) has bilateral parieto-occipital and mesial temporal defects on brain SPECT above. His total renal function is normal (serum creatinine 0.8 mg/dl); however, he has atrophy and decreased perfusion (without renal artery stenosis) of one ptotic kidney and also has stable angina (dyspnea on exertion) documented by inferoapical ischemia on cardiac stress testing with perfusion SPECT. His CR is abnormal (57.93-57.24)% < 3, typical of diabetics without renal failure.(70% ??? Of whom have abnormal CR).

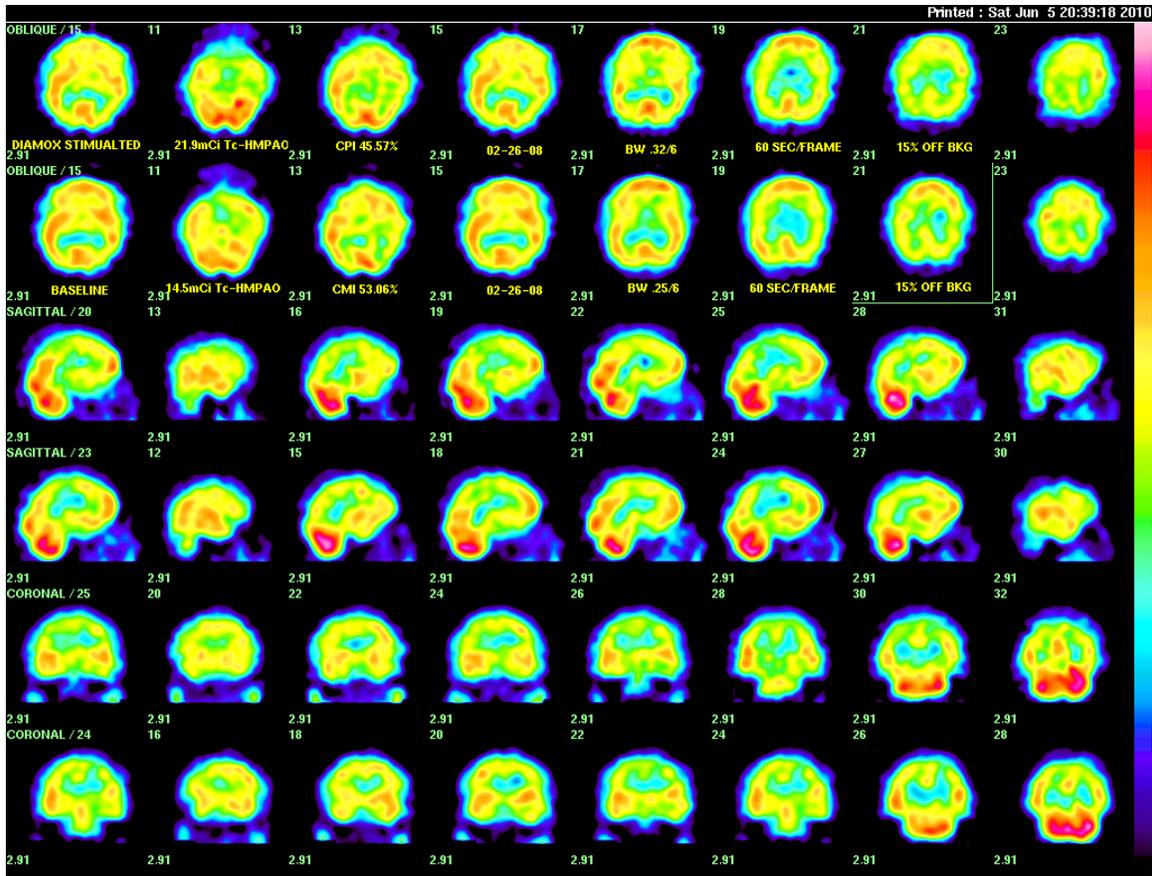


Fig. 4c: A 44 year-old type 1 diabetic man with HbA1c 9.1% with altered states of consciousness, including somnambulism, had basal brain SPECT (bottom of each of 3 rows of paired images, above) and acetazolamide-stimulated brain SPECT (top of each of 3 rows of paired images, above). Findings include patchy temporal distribution, common in seizures and altered consciousness states, decreased parietal activity between the anterior and middle cerebral areas and abnormal CR = (45.57– 53.06)% << 3%. After cilostazol 50 mg oral twice daily, increased insulin with carbohydrate counting and an insulin pump, lisinopril 10 mg oral daily to prevent nephropathy (even though normotensive), and caseomg smoking 1.5 packs per day of cigarettes, his renal function remained normal (serum creatinine 1.14 mg/dL) and HbA1c decreased to 7.5%.

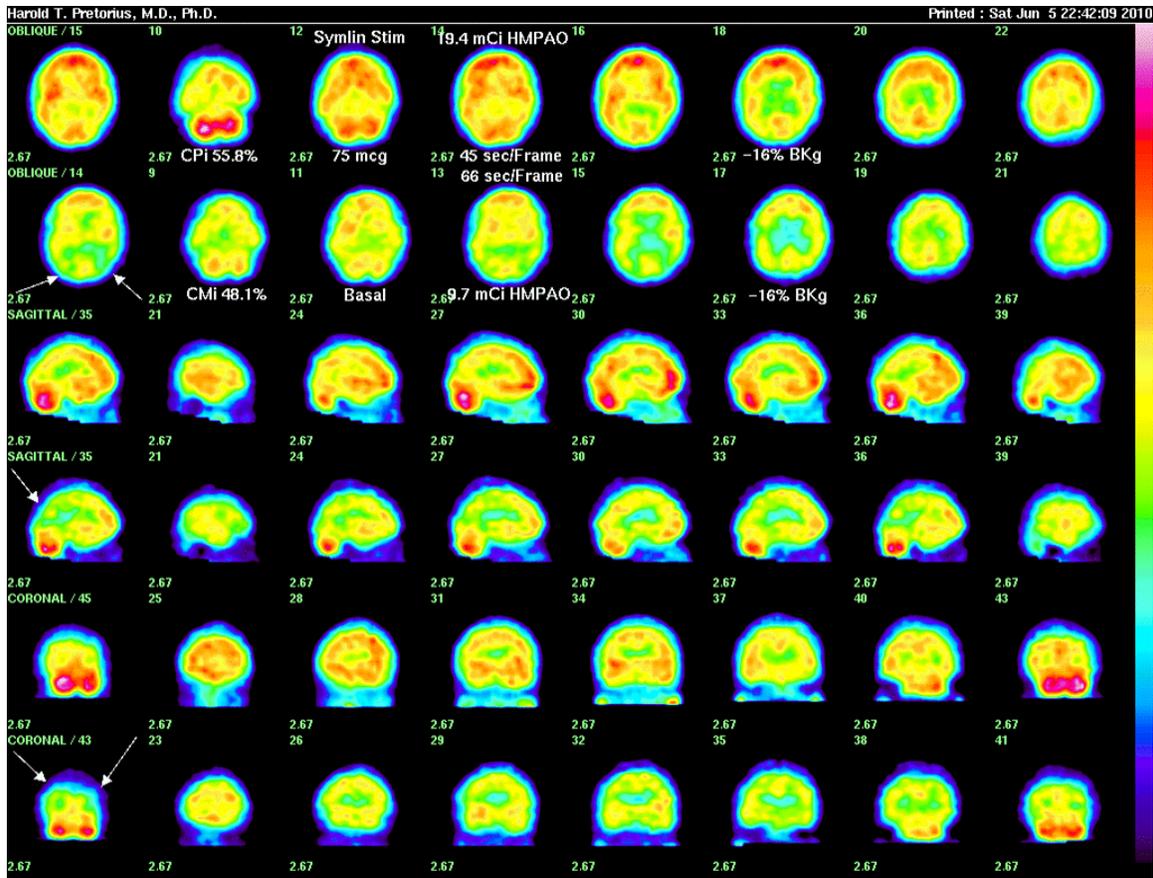


Fig. 4d : Now 46 years old, the usually well-controlled type 1 diabetic man develops an upper respiratory illness which exacerbates his glycemic control. At basal brain SPECT (bottom of each of 3 rows of paired images, above) his blood sugar was 296 mg/dl. Perfusion deficits are evident in the parieto-occipital cortex bilaterally (white arrows) as well as patchy temporal and parietal areas similar to his prior scan (above on left). After only 3 units insulin acutely to gradually reduce his blood sugar to 193 mg/dl over about 90 minutes, his Symlin (total dose 75 mcg) stimulated brain SPECT shows remarkable resolution of abnormalities and normalization of CR to (55.8 minus 48.1)% > 3%, essentially reversing the abnormal CR present 2 years earlier (Fig 4c, above, left).

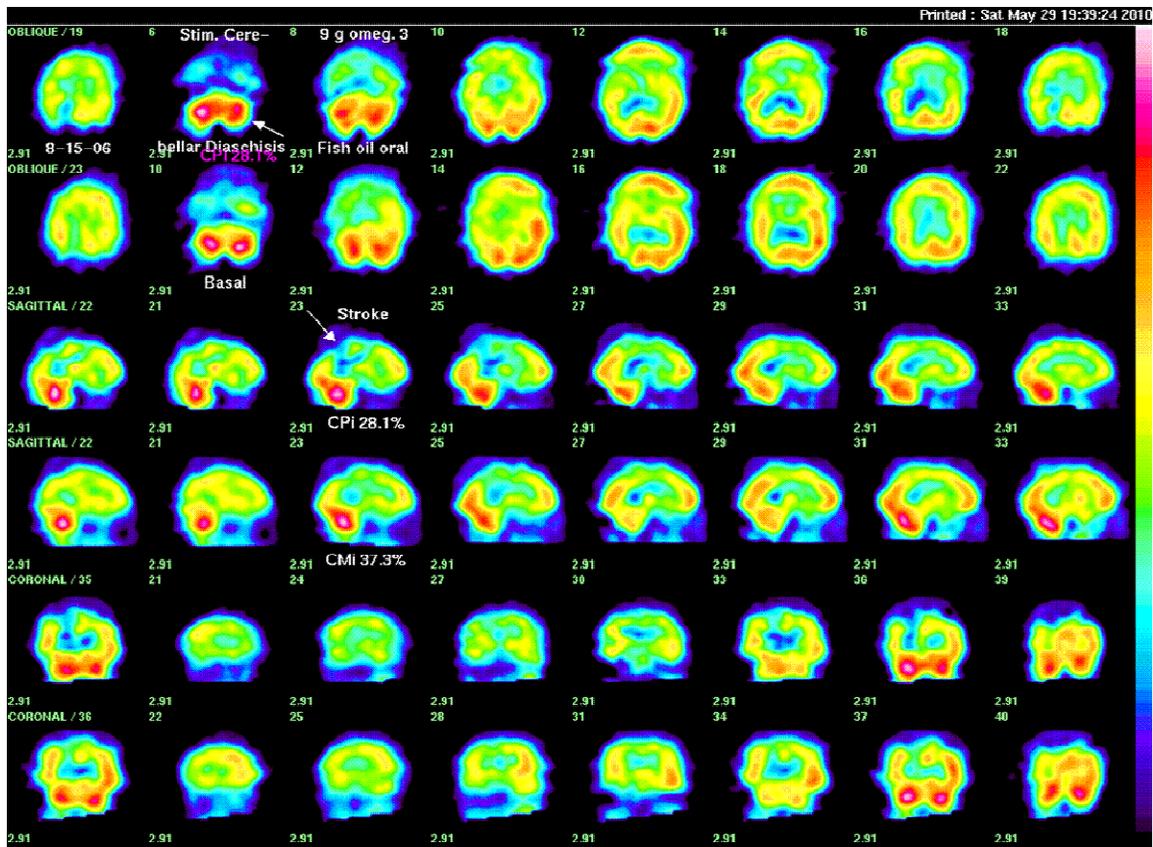


Fig. 5: An 86 year-old woman with renal failure, serum creatinine 2.6 g/dl, cystatin C 2.75 and GFR 22 ml/min, exemplifies exception to the usual preservation of CRi with renal failure. The top row of each set of 3 paired images is post perfusion stimulation, which was 10 capsules of fish oil in this case, which we have repeatedly shown is similar to either acetazolamide IV or nitroglycerin sublingual. A right posterior parietal stroke is easily appreciated. Saggital image 23 shows further decreased perfusion in the penumbra area as compared to the basal images below. Of 19 patient scans (19/73 = 27% of all renal failure scans) with renal failure who had abnormal decrease in CR (i.e. < 3%), there were 11 instances (8 patients) of stroke, or 57.9% (13/19) of such cases.

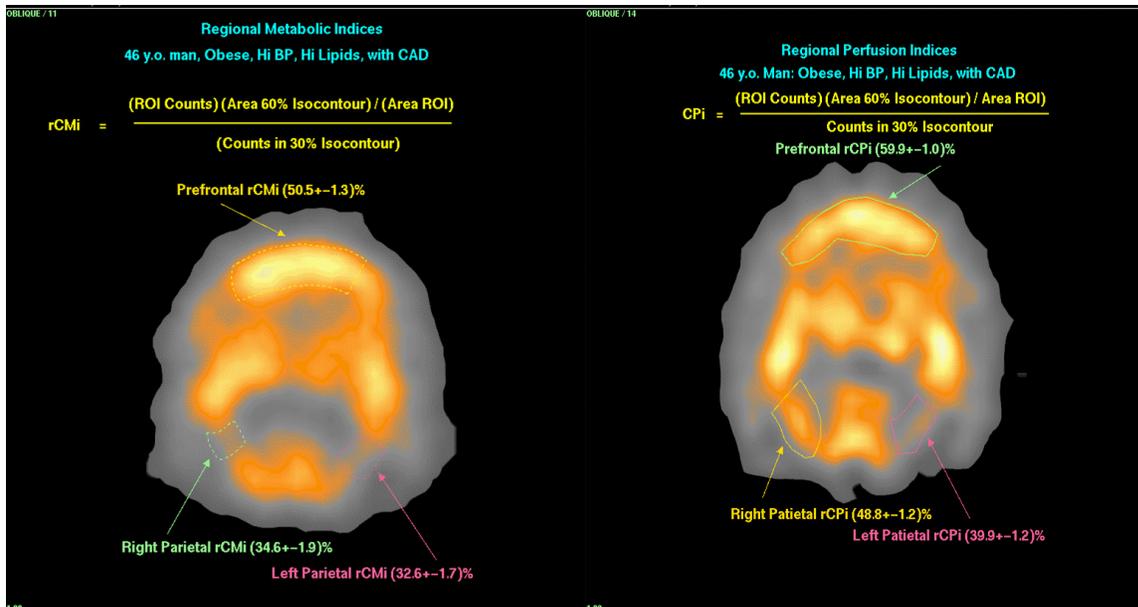


Fig. 6a : Regional Metabolic and Perfusion indices are shown to the right using a hot metal color scale (golden white, most activity and light gray, least activity) for the Brain SPECT in Fig. 6c, below on the right. The uncertainty in these indices depends mainly on the Poisson counting statistics for the smaller individual regions of interest (ROI's). The normal range for regional metabolic or perfusion indices calculated as shown is only slightly broader than the normal range for CMi, approximately 50% to 72% or CPi., approximately 53% to 75%. This way of analyzing ROI's avoids ambiguity of right to left comparisons with diseases such as Alzheimer's disease, which often involve bilateral deficits, and has the intuitive appeal of similar numerical comparisons.

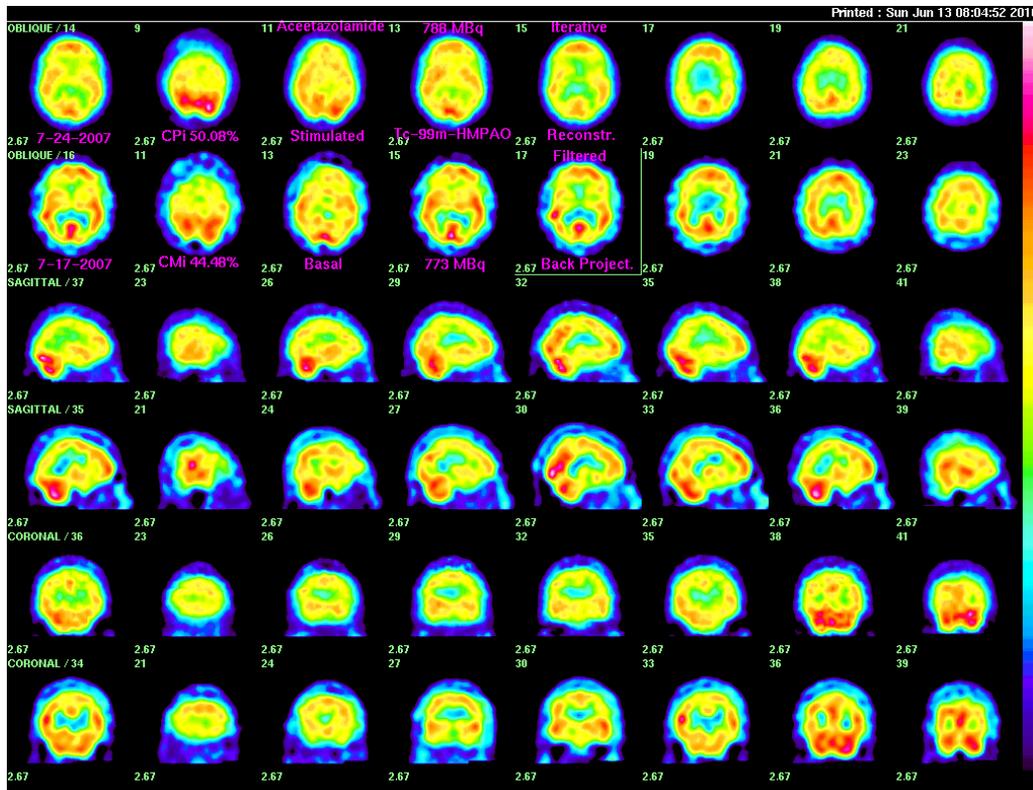


Fig 6b: Brain SPECT above with acetazolamide-stimulated perfusion (top of each of 3 paired rows of images) for a 43 year-old morbidly obese and insulin resistant man with normal renal function and normal CR (50.08-44.48)% >3%, although at least 64% (32/50) of insulin resistant nondiabetics with normal renal function in this study had abnormal CR. Additional factors often associated with obesity which may have contributed to abnormal CMI in this patient include: hyperlipidemia, particularly hypertriglyceridemia, low HDL cholesterol, hypertension, sleep apnea and exercise-induced angina. He also had coronary artery disease, his coronary angiogram showing stenosis of a diagonal branch of the left anterior descending coronary artery. The patient was informed by multiple cardiologists that coronary angioplasty of the proximal branch artery occlusion would be technically difficult and that he should consider coronary artery bypass graft surgery; however, he declined surgery to pursue aggressive medical management.

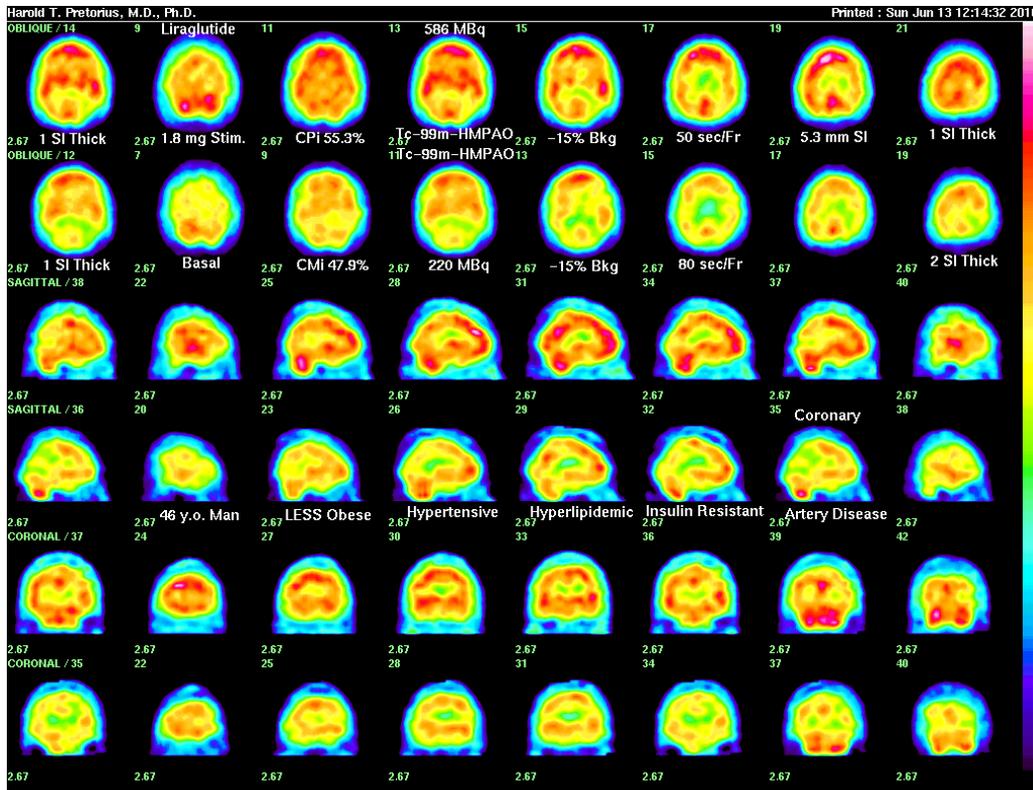


Fig. 6c: Follow-up brain SPECT using liraglutide perfusion stimulus for the now 46 year-old man whose earlier scan is shown in Fig 6b, above to the left, who now exercises regularly, has lost over 30 lb, takes rosuvastatin 20 mg each evening), multiple antihypertensives including an angiotensin receptor blocker (valsartan 320 mg), a diuretic (hydrochlorthiazide 12.5 mg), and a beta blocker (nebivolol 20 mg). His triglycerides are not improved by an Atkins diet and his left anterior descending coronary artery branch has occluded, resulting in a minor myocardial infarction. Despite improved CMi and CPI with still normal CR, this patient has progression of minor parieto-occipital deficits shown by regional CMi and CPi in the illustration above this panel (Fig. 6a). Improvement in these parieto-occipital deficits with liraglutide contributed to the patient's physicians opinion that liraglutide (U.S. FDA approved for type 2 diabetes therapy) was a more appropriate weight loss adjunct than an Atkins diet for this insulin-resistant, hypertriglyceridemic individual.

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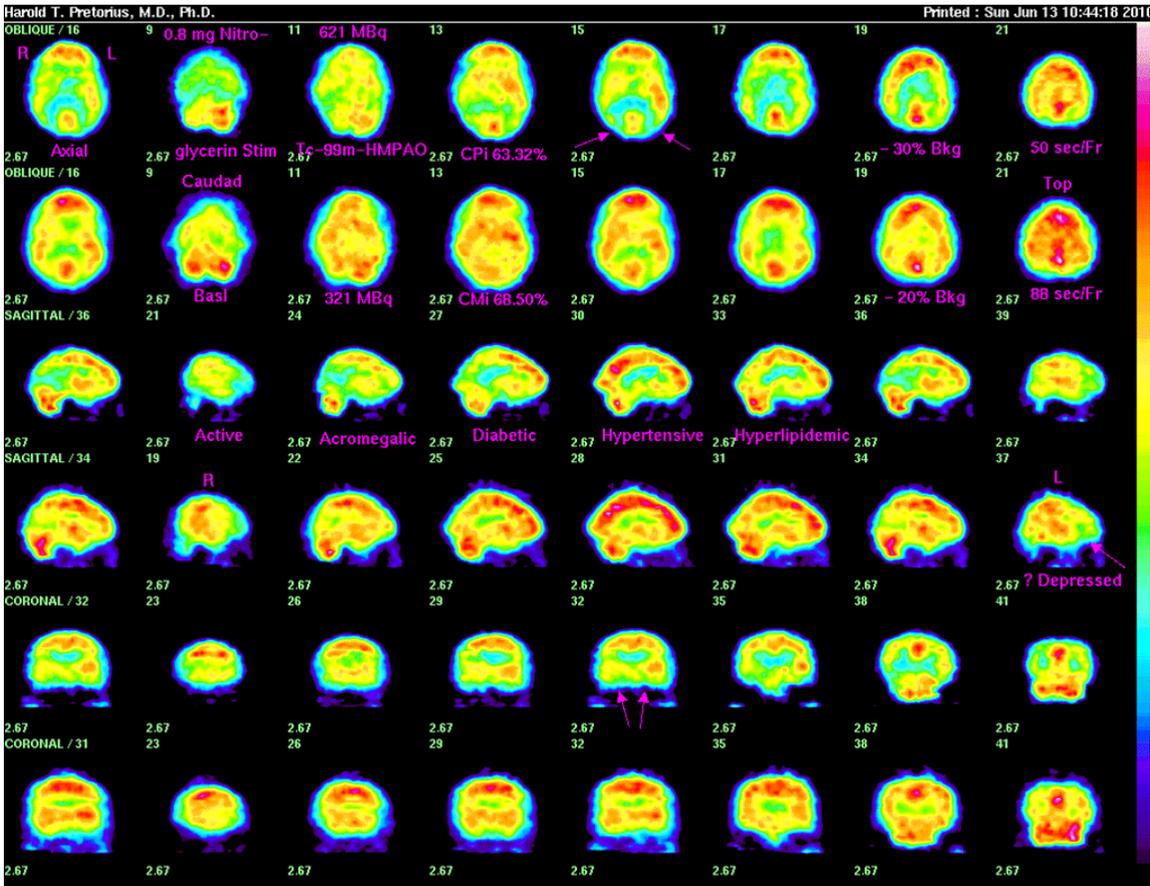


Fig. 7a: Acromegalic 62 year-old man, post hypophysectomy, with persistant pituitary tumor activity documented by incompletely suppressed somatomedin C (Insulin-Like Growth Factor 1) 283 ng/ml (normal 76-212 ng/ml) by Somatulin therapy has mild cognitive impairment (short-term memory loss requiring frequent notes) and renal insufficiency: serum creatinine 1.61 mg/dl and GFR 44 ml/min. Multiple metabolic risk factors including active pituitary disease, hypertension, type 2 diabetes mellitus and hyperlipidemia appear to overcome the usual effect of renal insufficiency to preserve CR, which is abnormal here since CPI 63.32% minus CMI 68.50% << 3%. Peak contribution of the basal image to the nitroglycerin-stimulated SPECT is 20%; however, only 10% additional background is subtracted beyond a scattering background taken as 20% here, which emphasizes bilateral parieto-occipital and mesial temporal deficits typical of amnesic mild cognitive impairment.

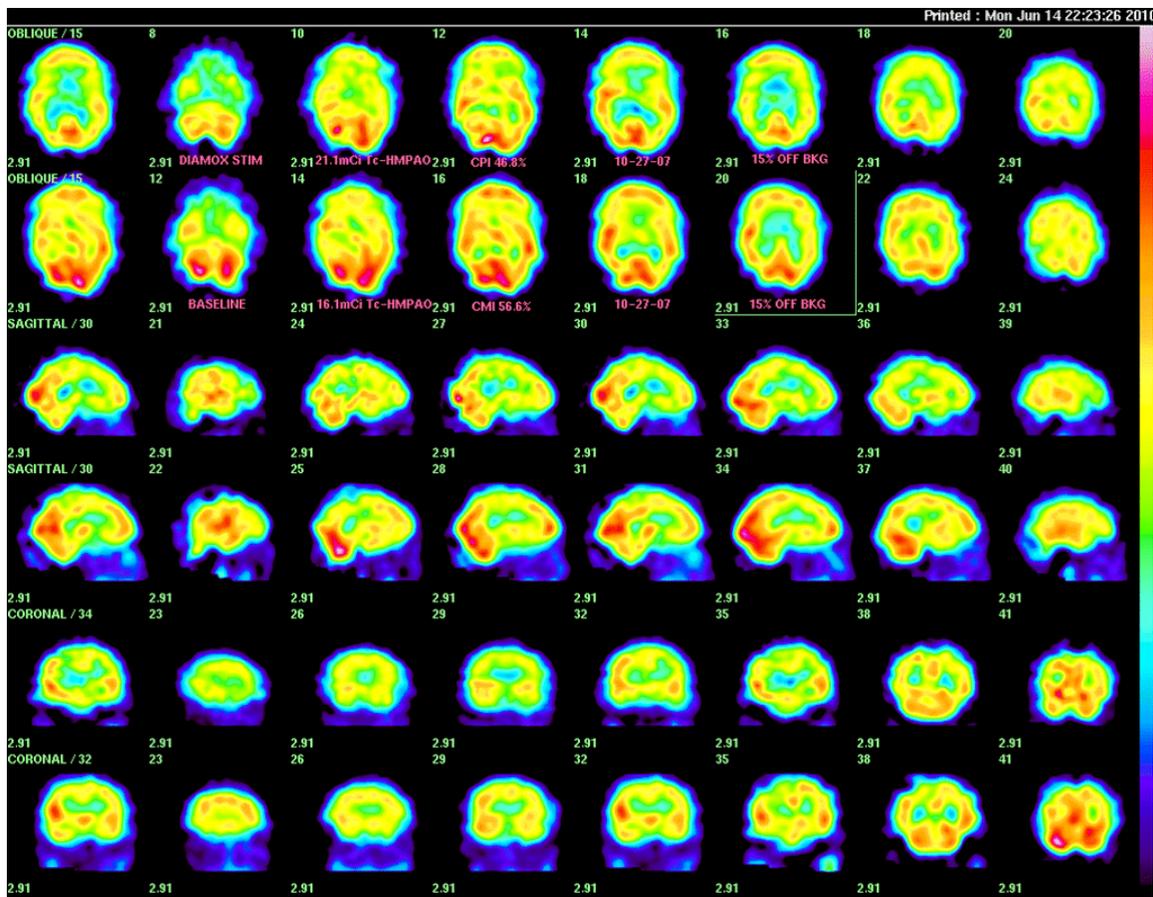


Fig.7b: Above are SPECT images for a 71 year-old hypogonadal, type 2 diabetic man with hypothalamic hypoperfusion and stable renal insufficiency, GFR (46.4+3) ml/min over 2 years, whose CR (46.8-56.6)% < 3 is also abnormal. Of a total of 4 pituitary patients with renal insufficiency, 75% (3/4) were exceptions to the usual observation of normal CR, these 3 together with 10 scans in 8 stroke patients (one of whom had pituitary apoplexy) accounting for 13/19 = 68.4% of the total number of such atypical cases.

Although not studied systematically in this work, both this patient and the pituitary patient shown in Fig 7a (above right) have minor left orbitofrontal deficits (arrow above right, sagittal image #37) and here, above, in 7b in sagittal images 36, 39 which may be associated with depression, perhaps yet another dementia risk factor which is certainly associated with diabetes mellitus and perhaps other dementia risk factors as well. We have observed (data not shown) that such deficits, even in patients with history of resistant depression, may resolve with incretin stimulation, specifically, pramlintide (Symlin) approximately 90 mg subcutaneously.