

Insulin Resistance and Diabetes Mellitus are Frequent Complications in Long Term Follow-Up of Patients with Traumatic Brain Injury

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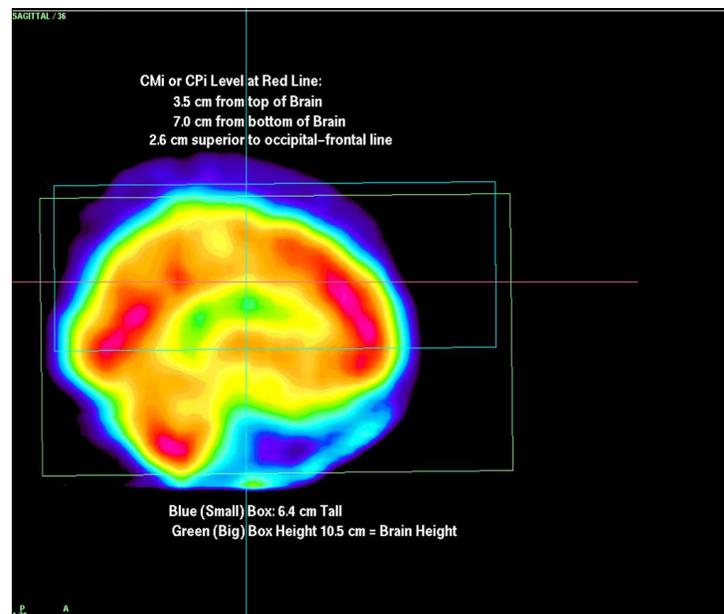


Fig. 1: Axial SPECT slices are defined parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of the normal-sized lateral ventricles. Activity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

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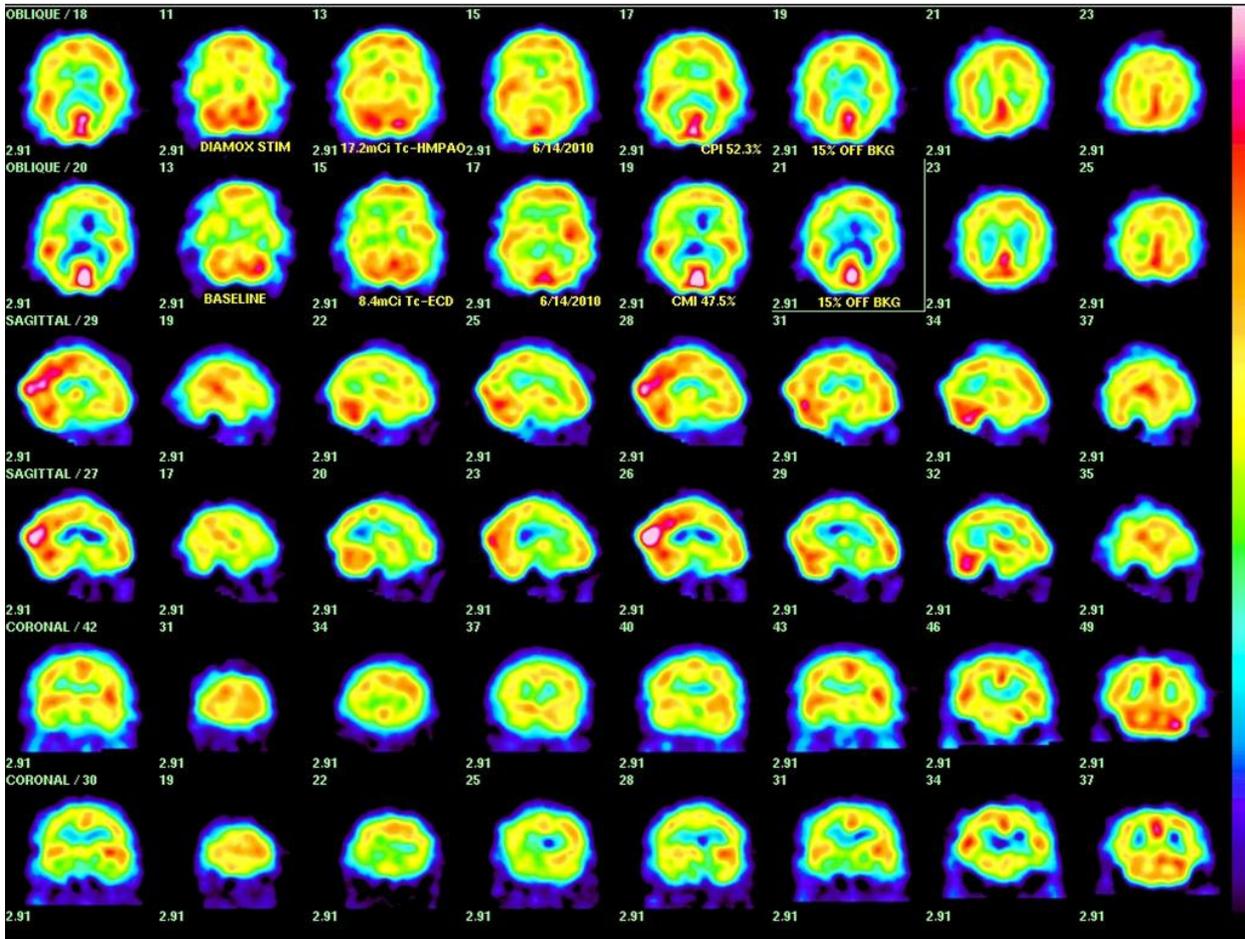


Fig. 2: SPECT for a 48 year-old insulin resistant man, basal images are displayed as the bottom of the three sets of paired images and were performed using Tc-99m-ethylcysteinate dimer which closely approximates FDG basal metabolic images. The perfusion-stimulated images (top of each of the three sets of paired images) were performed after 500 mg IV acetazolamide using the SPECT perfusion tracer Tc-99m-hexamethylene amine oxime. Features of TBI include the mesial temporal metabolic and perfusion tracer deficits, seen well especially on the right in the coronal images, the left orbitofrontal hypometabolism, seen well in the sagittal images (often correlated with depression, which the patient also had), basal ganglia hypometabolism, frequently seen in pituitary disease, also seen well in the sagittal images, and bilateral parieto-occipital hypometabolism. This patient had normal cognitive function (TYM 47/50) and has cerebral flow reserve comparable to near normal patients. Patients with compromised cognition often have abnormally decreased cerebral flow reserve, lower CMi, and more prominent bilateral mesial temporal deficits.

This patient developed insulin resistance 23 years after his first of two concussions, the first one a motor vehicle accident and the second a year later when a heavy object fell on his head. He also developed a 7 mm pituitary micoradenoma (prolactinoma with serum prolactin up to 137 ng/ml) approximately 10 years after developing insulin resistance.

In our overall series of 330 patients with traumatic brain injury, 8 patients had brain tumors, 6 of these being pituitary adenomas, one being a third ventricle tumor and the other a deep brain low grade glioma. All of these patients have at least one pituitary insufficiency syndrome except for the deep brain glioma patient, who developed cyclic Cushing's disease. The incidence of $8/330 = 2.4\%$ is within the broad incidental intracerebral tumor incidence reports indicating no definite evidence of TBI contributing to pituitary disease. Clearly, most pituitary disease after TBI is not due to pituitary tumors. However, pituitary insufficiency syndromes including adrenal ($13/157 = 8.2\%$) and growth hormone ($9/157 = 5.7\%$) insufficiency would be likely to impede development of insulin resistance or type 2 diabetes mellitus, at least one of which was eventually observed in 80.0% of the 157 patients in this series.

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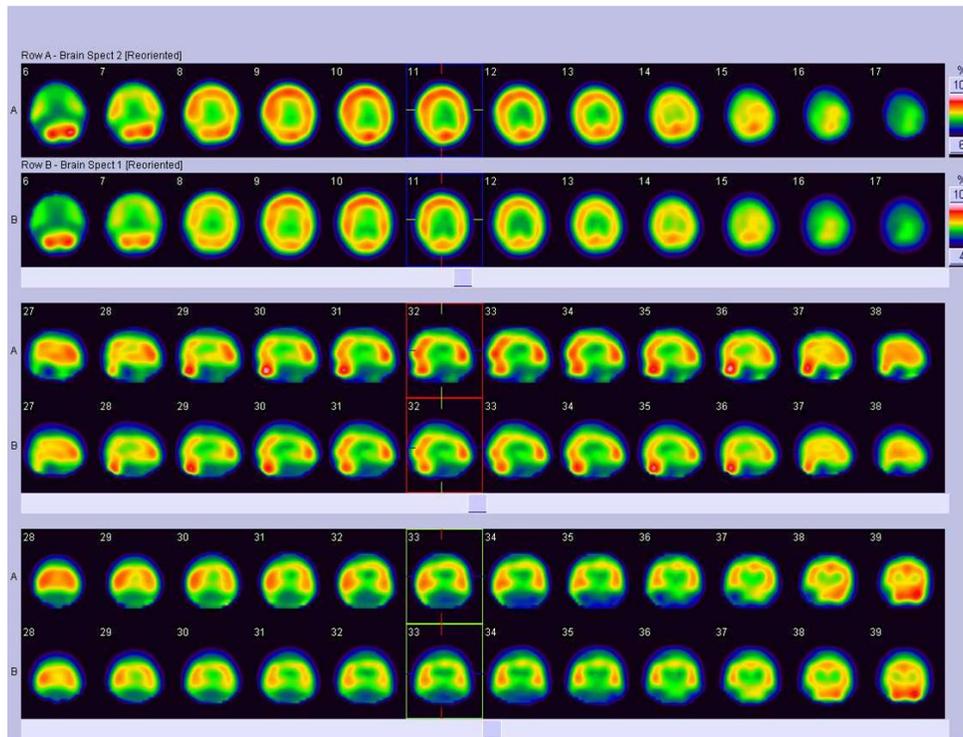


Fig. 3. Basal and perfusion stimulated brain SPECT for a 32 year-old woman who had a left temporal skull fracture at age 17 years, requiring a steel plate to stabilize, but remarkably suffered no demonstrable injury to the left cerebral hemisphere and instead suffered right parietal contrecoup injury. This is demonstrated as decreased right parietal tracer distribution. Her CMi 47.8% was borderline low and CPi 55.9% comparable to near normal patients. Neuropsychological testing by two independent psychologists agreed in detecting isolated right parietal deficits.

Her TYM was 39/50, normal 47+2 and mild cognitive impairment (MCI) was confirmed by modified fractal analysis showing SN 0.45 for the CMi and 0.56 for the CPi vs. 11 near normal patients with average SN 0.35+0.05 and 18 MCI patients with average SN 0.59+0.08.

This patient remarkably had type 1 diabetes prior to her TBI; and at weight 115 lbs had no evidence of insulin resistance. She gained weight by age 30 years, which was 13 years post TBI when her waist increased to 34 inches at weight 142 lbs, height 65 inches. Factors possibly contributing to more rapid development of IR included positive family history of type 2 diabetes in both her grandmothers and a paternal uncle, personal history of gestational diabetes at age 31 years and intermittent hypercortisolism with morning serum cortisol up to 46.7 mcg/dl (normal 6.2 to 19.4 mcg/dl) as well as hepatic steatosis. Her serum cortisol was dexamethasone suppressible and she has no other evidence of an adrenal nor pituitary tumor.

SUMMARY

The table below summarizes data for 157 patients who had TBI with long term follow-up but did not have IR or type 2 diabetes mellitus at the time of TBI. Remarkably, over an average follow-up of 24.8 years, only 20% of the patients avoided development of either type 2 diabetes or IR. Despite the broad standard deviations noted and many biological variables involved there is unquestionably a longer lag time to development of 33.3 years to develop diabetes than the 18.4 years to develop IR ($p < 0.0000001$). The cognitive function, monitored by TYM (normal range 47+-2) is also significantly different for diabetics who were more compromised than IR ($p = 0.0016$) or those without DM or IR ($p = 0.0000031$). Compromised cognitive function also correlates with abnormal FRi (last table column) Pituitary disease is of similar frequency in IR as patients without IR or DM but higher, over 50%, in those with DM . Strokes are about twice as prevalent in diabetics as those with IR and nearly three times more prevalent in diabetics than those without IR or diabetes. Seizures were remarkably similar in all three groups.

	# of patients	Yrs From TBI	TYM	Stroke	Depression	Seizures	Pituitary	Opiates	% of Total Patients	FRi
TBI with IR	77	18.38+/-11.78	44.39+/-2.97	9.09%	35.06%	5.19%	36.36%	18.18%	48.39%	0.07+/-6.33
TBI with DM	49	33.27+/-14.85	42.00+/-4.54	18.37%	34.69%	8.16%	51.02%	30.61%	31.61%	0.21+/-6.47
TBI without IRS or DM	31	22.89+/-19.23	46.55+/-2.73	6.45%	45.16%	9.68%	45.18%	19.35%	20.00%	3.48+/-6.94