MILD HYPERTHYROIDISM CAUSES A PSEUDO-ALZHEIMER’S PATTERN OF CEREBRAL METABOLISM WHICH IS REVERSIBLE WITH CEREBRAL PERFUSION STIMULANTS

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Abstract

Objective: Compare cerebral metabolism in hyperthyroidism and Alzheimer’s disease.

Methods: Brain SPECT used 12 to 25 mCi Tc-99m-HMPAO intravenous (IV) in a dark, quiet room. Basal perfusion served as a marker of metabolism. Cortical metabolic and perfusion indices (CMi and CPI) compared patients before and 1 hr after Mona Vie (acai fruit juice) or known cerebral perfusion stimulants: 500 mg acetazolamide IV or 0.6 mg nitroglycerin sl in 15 min or 10 g fish oil (Lovaza) oral in 3 hrs. Normal CMi (61+-10)% and CPI (65+-9)% were from 20 patients with minor complaints and low likelihood of disease.

Results: Decreased memory was noted in 3 hyperthyroid patients, 1 with toxic nodular goiter and 2 with Graves’ disease, without evidence of coexisting Hashimoto’s thyroiditis, who had borderline low CMi (50+-5)% but significant regional parieto-occipital and mesial temporal defects, defined by regional CMi (40+-8)%, calculated as the product of regional activity and the ratio of active global (in a 60% isocontour) to regional cortical areas, divided by total cerebral activity (in a 30% isocontour). The similar Alzheimer’s pattern in 2 cases was more pronounced, with much lower CMi and regional CMi of (30+-10)%. In early Alzheimer’s and in hyperthyroidism the regional perfusion defects resolved with Mona Vie or any of the other perfusion stimulants, resulting in normal CPI (58+-5)%. There was no consistent effect on patient symptoms within several months of therapy with Lovaza; however, symptoms tended to remit after successful therapy of hyperthyroidism.

Discussion: Multiple reports from the prospective Rotterdam study show a > 300% increased incidence of Alzheimer’s disease in hyperthyroidism, the mechanism of which is unknown, but from the results here likely involves specific cerebral metabolism defects. Epidemiological studies suggest lower rates of Alzheimer’s disease with increased fish consumption, although more recent reports question if the beneficial effects of natural fish may be compromised by increasing levels of neurotoxic pollutants, such as mercury. It is intriguing that multiple mechanisms, including dependence on prostaglandins (fish oil), nitric oxide (Mona Vie and nitroglycerin), and carbonic anhydrase inhibition (acetazolamide) all similarly stimulate cerebral perfusion.

Conclusion: Hyperthyroidism causes a pseudo-Alzheimer’s pattern of abnormal cerebral metabolism which resolves with either natural or pharmacologic cerebral perfusion stimulants, independent of their mechanism of action.
A 55 year-old diabetic woman’s normal brain SPECT is shown on the right. The perfusion-stimulated study is shown in each of the top row of the three paired images. In this case, cerebral perfusion was stimulated with two doses of 0.4 mg nitroglycerin sublingual. Diabetics may have up to three areas of decreased regional perfusion; while, nondiabetics have only one. Thus, this study is well within normal limits even though the patient is insulin dependent and hypertensive. Other normal aspects of her study include peak tracer distribution in the posterior cingulate.
On the right is a 70 year-old patient’s basal brain SPECT showing an actual Alzheimer’s pattern, with more pronounced abnormalities than the pseudo-Alzheimer’s pattern noted in patients with mild hyperthyroidism. Quantitative indices for actual Alzheimer’s disease are much more markedly abnormal. In this case the Cortical Metabolic index was near 20%, as compared to normal approximately 50-72%. This patient’s Mini Mental Status Examination was 9 of 30, also consistent with moderately severe dementia. Note that salivary activity is high relative to her brain!
A 21 year-old woman with memory loss and confusion (MCI) has borderline hyperthyroidism evidenced by borderline high 24 hour thyroid iodine uptake of 30% at 24 hours (shown below) and a subtle suggestion of a warm nodule in the superior portion of the left lobe, shown in the left anterior oblique projection below. Her basal brain SPECT (lower of the three paired rows) scan shows temporal lobe and left parieto-occipital regional abnormalities consistent with a pseudoAlzheimer’s pattern which improves after 10 grams oral fish oil. The antithyroid antibodies were negative.
A 72 year-old mildly hyperthyroid, type 2 diabetic woman has recovered from hyperthyroidism, perhaps due to concurrent Hashimoto’s thyroiditis and now has a normal I-123 thyroid scan and uptake of 9.8% at 4 hours, shown on the right. Her pseudoAlzheimer’s pattern of decreased brain metabolism (inferior of each of three rows of SPECT paired images) is improved both by IV acetazolamide (above image on right) or oral Mona Vie (acai berry juice) as shown above on the left. She has also had stroke-like symptoms, reminiscent of Hashimoto’s encephalopathy, and stage I hypertension, controlled on an ARB/calcium blocker.
A 36 year-old woman had hyperthyroidism controlled on methimazole but has memory loss and confusion as well as unsteady gait. Workup for multiple sclerosis was negative. Her basal brain SPECT (lower of three paired rows to the left) shows decreases right parieto-occipital, left parietal and temporal which are resolved with acetazolamide (upper of three paired rows to left). A minor positioning artifact between the basal and post perfusion stimulation scans (more upward tilting of the frontal cortex in the basal scan) has little effect on normal CMi and CPI indices.

Hyperthyroid 27 year-old woman with Graves’ disease and high 4 hr I-123 uptake 18% (on right), complained of memory loss consistent with MCI. Her acetazolamide-stimulated brain SPECT (top of each of three paired images to right of her thyroid scan) is shown over the basal scan. Note the pseudo Alzheimer’s pattern of bilateral decreased parieto-occipital tracer distribution in the basal images which is improved with acetazolamide IV. The patient took Lovaza (omega-3 unsaturated acid ethyl ester of marine origin, i.e. fish oil) 4 gram oral daily for 4 months as well as methimazole 15 mg daily and her symptoms of hyperthyroidism and memory loss resolved completely.
A 40 year-old intellectually gifted woman complained of memory loss and confusion which was initially diagnosed by her neurologist as due to depression alone which is associated with decreased orbitofrontal tracer distribution in the brain SPECT scans shown above from 2006 on the left and 2007 on the right. She had severe migraine and experienced a minor left parietal stroke, confirmed on MRI in 2001. Although initially hypothyroid, she preferred a higher thyroid dose and was only gradually titrated to a normal TSH over the interval between the two above SPECT scans, the one on the left used omega 3 unsaturated fish oil (10 grams oral) to stimulate perfusion, while the one on the right used 0.4 mg nitroglycerin sublingual. The patient took Lovaza (prescription fish oil) between the two scans and gradually improved; however neuropsychological tests obtained recently confirmed persistent deficits in expressive aphasia, motor skills with the right arm and hand more compromised than the left, and unipolar depression. Although not optimal for pre and post comparison, the two methods shown are illustrative, the basal ethylenecysteinate dimer (Neurolite) study being arguably a more true metabolic tracer (more similar to fludeoxyglucose) than basal studies with the more pure perfusion tracer, hydroxymethyleneamine oxime (Ceretec), shown in the lower paired images the left.
45 year-old hyperthyroid (Graves’ disease) woman has memory loss and confusion with cognitive exam complicated by concurrent bipolar affective disorder, treated with lithium 300 mg po bid and Seroquel 150 mg po qhs. The two brain SPECT scans above both used nitroglycerin sublingual for perfusion stimulation, shown in the top row of each of the 3 sets of paired images, the ones on the left obtained one year before those on the right. She was advised to take Lovaza fish oil owing to stimulated perfusion tracer deficits which in our experience respond even better to such therapy than more prominent basal deficits. Unfortunately her insurance did not cover Lovaza and she only took over the counter fish oil briefly. Despite control of mild hyperthyroidism (T3 2.04 with nml 0.6-1.8 and TSH < 0.01 with nml 0.35-5.5) with methimazole, her follow-up brain SPECT reveals development of a pseudoAlzheimer’s pattern and her symptoms of memory loss and confusion worsened. Comorbid conditions included hyperlipidemia (Total cholesterol 230, LDL 176, triglyceride 135) also treated intermittently with statins and Zetia, both of which she tolerated poorly, diverticulitis and irritable bowel syndrome, treated with nortriptyline 25 mg po qd. Her case raises suspicion of whether an earlier stage of eventual metabolic encephalopathy may involve initial hypoperfusion, which if untreated, may progress to subsequent more prominent metabolic deficits and associated more prominent cognitive symptoms.
Summary

The true incidence of a pseudo-Alzheimer’s pattern of brain metabolism and perfusion in hyperthyroidism cannot be ascertained from a small series of patients; however, we find that the pattern is certainly not uncommon among hyperthyroid or recently hyperthyroid patients with cognitive complaints. Of particular interest is the concept of mild cognitive impairment (MCI) which parallels the concept of insulin resistant syndrome (IRS). Thus, our results suggest that just as patients with IRS have an increased risk of diabetes mellitus, patients with hyperthyroidism and presumably MCI associated with a pseudo-Alzheimer’s pattern of cerebral perfusion and metabolism have a clearly increased risk of Alzheimer’s (350% increased per the Rotterdam study). Nonetheless, in neither case is there uniform progression, either of IRS to diabetes mellitus, nor of MCI, at least that associated with hyperthyroidism, to true Alzheimer’s disease.

The reasons may be similar in the sense that MCI may be a form of cerebral insulin resistance, demonstrated by decreased brain glucose metabolism, typically first affecting mesial temporal and parieto-occipital cortex. Remarkably, this pattern, at least in its early stages, is reversible or nearly reversible, with multiple agents that improve cerebral perfusion by different mechanisms, being nonetheless effective. We are particularly encouraged by improvement in cerebral metabolism associated with relief of memory loss in patients after fish oil or Mona Vie therapy.