Vascular Dementia Pathophysiology Defined by Brain SPECT Response to Stimulating Cerebral Perfusion


Abstract

Background: Significant cognitive loss usually has at least two causes, typically VaD and neurodegenerative/metabolic. We define the VaD component by its acute response to stimulating cerebral perfusion

Aims: Correlate SPECT measures of brain perfusion and metabolism with putative VaD therapies/comorbidities: 1) Anticoagulants, antihypertensives, antiplatelets, endocrinologic agents, statins; 2) Brain perfusion stimulants: cilostazol, nitrates, omega-3 fish oil; 3) Comorbidities: cardiac disease, diabetes mellitus (DM), metal toxicity, neuropsychiatric, thyroid (TD) or renal disease (RD).

Methods: Brain SPECT at clinically relevant intervals used 0.4-0.8 mg nitroglycerin sl or similarly effective stimulants and calculated indices of perfusion (CPi) and metabolism (CMi). Metal burden was monitored by fractionated urine porphyrins and RD by GFR calculated by blood test or renography. Therapies including prescribed diet, exercise and polypharmacy were comprehensive but variably accepted.

Results: VaD and comorbidity correlations are both dynamic (minutes/hours) and long-term (months/years). Abnormal urine porphyrins affect > 15% of >200 patients and robustly relate (p < 0.02) to CPi, except for DM. VaD associates with DM, TD and depression, which if bipolar, relates remarkably to toxic metals (p < 0.01). Among > 100 patients on aspirin and clopidrogrel, two had hemorrhagic strokes; there was no other hemorrhagic event among > 100 patients on cilostazol and/or omega-3 fish oil. Among patients with CPi < CMi > 30%, response to vascular therapy more often increases CPi than CMi.

Conclusion: Brain SPECT sensitively relates VaD severity to its comorbidities. For
early to moderate pathophysiologic deficits amenable to current therapy, VaD is more responsive than metabolic/neurodegeneration.

1. Cortical Metabolic indices were calculated from basal SPECT images using an IV metabolic tracer such as 200 MBq F-18 fluorodeoxy-glucose, 560 MBq Tc-99m-ECD or 500 MBq Tc-99m-HMPAO IV, given in a quiet, dark room. The dual-head SPECT camera had 5.5 mm resolution using ultra-high resolution parallel-hole collimators, sensitivity 6500 cpm/MBq. Image matrix was 128 x 128 acquired in 64 frames/180 deg with 5 to 60 sec/frame (acquisition time usually < 30 min with iterative, nonlinear least square reconstruction). Cortical Perfusion indices were similarly calculated using IV perfusion tracers such as Tc-99m-HMPAO or Tc-99m-ECD (within the first few min for Tc-99m-ECD for perfusion data) and cerebral perfusion stimulants such as 0.8 mg nitroglycerin sl (1 to 2 min prior to IV tracer) 0.5 to 1.0 g acetazolamide IV (15-20 min prior to IV tracer), 10 g omega-3 unsaturated fish oil oral (3 hr prior to IV tracer) or 100 mg cilostazol oral (1 hr prior to IV tracer).
2. Below on the left is brain SPECT, perfusion-stimulated the top of each of the 3 rows of paired images, for a 69 year-old hypertensive man with history of TIA who has stable CPi 35.0% and repeat after two years of therapy with omega 3 fish oil and clopidogrel shows a similar CPi 35.5%, defining the level of CPi below which improvement with current therapies is unusual.

Below on the right is brain SPECT, similarly formatted with perfusion stimulated over the basal images for a 48 year-old man with trisomy 21, demonstrating more marked compromise of CPi 49.8% vs. CMi 54.7%, implying that the metabolic abnormality may be secondary to the perfusion deficit in Down’s syndrome.

3. A 62 year-old insulin resistant, hyperlipidemic patient, disabled due to memory loss on neuropsychological tests, has brain SPECT, below on the on the left, showing perfusion stimulus effect of antihypertensives. Resting BP 158/90 for the basal scan improved to 148/86 for the stimulated scan two days after aliskirin 300 mg and telemisartan 80 mg oral daily, which we have also observed within an hour of acute BP control, comparable to other acute perfusion stimuli, favoring a same day protocol without change in BP or other physiologic variables.

Below on the right is brain SPECT for a 65 year-old hypertensive, hyperlipidemic, insulin-resistant man whose CPi 44.1% decreased vs. CMi 46.9% with acute decrease in BP from 142/90 to 130/82. Remarkably, the same fraction, 68.7% of insulin resistant patients and diabetics have CPi < (CMi + 5)%.
4. Traumatic brain injured patients initially showed significantly less marked abnormality in cerebrovascular flow reserve than diabetics; however, with further study the difference was spurious: in fact among 35 traumatic brain injured patients, 25 had CPi < (CMi +5), or 71%, not statistically different than the 69% of diabetics or those with insulin resistant syndrome. Below on the right are SPECT images (perfusion-stimulated over basal for each of 3 rows of paired images) for a 62 year-old dizzy, depressed patient whose initial CPi 42.8% and coproprophorin I+III 123 mcg/L improved to CPi 47.9% and Coproporphyrin I+III 38 eight months after DMPS (rectal suppository chelation). Her initial CMi 55.6% decreased to 51.9% with therapy. Below on the right is the relation of CPi on the ordinate vs. total coproporphyrin I+III on the abscissa for 116 nondiabetic patients prior to any specific therapy. The patient’s response is below but comparable to the regression line.
5. Below on the left is Tc-99m-HMPAO brain SPECT, acetazolamide-stimulated on top and basal on the bottom of each of 3 paired image rows for a 40 year-old man with stiff-person syndrome whose CMi 50.1%, CPi 44.2% and corpromorphyrin I+III 78 mcg/L suggest oxidant stress mediated vascular pathophysiology.

Below on the right is similarly displayed brain SPECT for a 53 year-old hyperlipidemic woman who had an initial CMi 47.3%, CPi 37.8% post a TIA, consistent with mainly vascular disease who was treated with antiplatelet (clopidrogrel 75 mg qd) and statin (atorvastatin 80 mg or rosuvastatin 10 mg) therapy for one year. Follow-up brain SPECT on the right below showed CMi 60.1%, CPi 53.1% when her TYM test was 50/50 (unusually good for an American!). We are hopeful that further improvement may ensue with cilostazol which was used as the perfusion stimulant in this study and has consistently been similar in our experience to other cerebral perfusion stimulants.

Summary
Perfusion-stimulated brain SPECT sensitively reveals patients who are apt to respond well to available perfusion stimulants. The clinical scenario in which a specific perfusion stimulant is used for SPECT and subsequently for therapy tends to not only define the pathophysiology but also enhances patient acceptance and adherence to therapy. Monitoring therapeutic response with reproducible and quantitative indices of basal and perfusion-stimulated brain SPECT provides an opportunity to objectively define pathophysiology commensurate with the clinical course of the patients and aids in selection of specific and effective therapies.