Major Existing and Emerging Hypotheses for LOAD

I. **Aging Hypothesis:** Considered the greatest risk factor for the development of LOAD.

II. **Cholinergic Hypothesis**: The earliest hypothesis and generated the first clinical treatment with anticholinesterase medication.

III. **Aβ cascade Hypothesis**: The mainstay hypothesis for at least 2 decades. A trigger that may be necessary but not sufficient.

IV. **Tau Hypothesis**: Neuronal loss – atrophy. Insulin resistance of importance in relation of dysfunctional glycogen synthase kinase (GSK3β) signaling, which allows for hyperphosphorylation of tau and misfolding aggregation of tau proteins with malfunctioning of microtubules and disturbance of neurotransmitters and mitochondria carrier functions from soma along axons to synapses.

V. **Inflammation Hypothesis**: Neuroinflammation and reactive gliosis are hallmarks of LOAD. Microglia activation in response to multiple stressors such as oxidative - nitrosative stress and cytokine neurotoxicity. Neuroinflammation – activated microglia in preclinical Western, *db/db*, and BTBR *ob/ob* models at 16-20-weeks of age thus far and in human patients.

VI. **Oxidative Redox Stress Hypothesis**: This is a ***HUGE** intersect with LOAD and may be the greatest and earliest

ROS beget ROS and aMt beget aMt via neuroinflammation and aMGCs and neurotoxic cytokines.

VII. **Hypometabolism Hypothesis:** Glucose metabolism Hypo- and Hyperglycemia. FDG-PET (Positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose) has become a valuable indicator for diagnosis of neurodegenerative diseases that cause dementia including LOAD. Dysfunctional Mt are a central and important finding in diabetic brains. Of importance is the BOLD PET scans and studies contribute data that are in addition to measuring the amount of glucose delivered as it also measures the CBF since the vasculature delivers glucose that is measured and delivered to regional brain areas.

VIII. **Genetic Hypothesis: ApoE-ε4** is the greatest genetic risk factor and various genetic single nucleotide polymorphisms (SNPs) and possibly maternal mitochondria inheritance may contribute to LOAD via the genetic hypothesis.

IX. **Vascular Hypothesis-** 2 Hit Hypothesis and the (micro)-vascular cognitive impairment and dementia (VCID) Hypothesis: These paired hypotheses have merged into accepted hypotheses in the present time not only for vascular dementia (VaD) but also LOAD.

X. ***Evolving hypotheses*:**

1. **Mitochondrial Cascade Hypothesis:** Rapidly emerging as a sustaining hypothesis.
2. **Microbiota-gut-brain-immune axis Hypothesis:** Most certainly this hypothesis will be equally accepted (as I-IX) over time and is definitely an exciting story to follow. Rapidly emerging as a sustaining hypothesis.
3. **Antimicrobial Protection Hypothesis:** Is emerging as a sustaining hypothesis.

Small vessel disease	Lacunes	EPVS	WMH	Cerebral Microbleeds
Location	Upper portions of Basal Ganglia thalamus, internal and external capsule, pons, and periventricular white matter.	Basal ganglia (BG) **Type I** Centrum semiovale (CSO) **Type II** Midbrain **Type III.**	Periventricular, deep white matter distinct from periventricular regions.	cortico-subcortical junction, and deep grey or white matter in the cerebral hemispheres, brainstem, and cerebellum
Morphology Shape	Irregular shapes, sharp edges, Or wedged shaped.	Well defined, round, oval, tubular.	Sharp edges, linear, and frequently follow the outlines of the adjacent ventricle. Elongated	Number (few or multiple); Rounded - smooth edges.
Symmetry	Asymmetrical.	Symmetrical.	Asymmetrical.	Asymmetrical.
Size	3-15mm diameter	1-3mm but no specific cutoff	3-12mm but may be larger; they are usually elongated	2-5mm in diameter (up to 10 mm)
FLAIR (fluid-attenuated inversion recovery)	(+) FLAIR (+) FLAIR usually reflects siderosis or Gliosis - reactive astrocytes or both	Primarily non-FLAIR	(+) FLAIR	Areas of signal void with Associated blooming seen As hypointense (dark) on T2*-weighted MRI
Clinical Significance	**Footprint of stroke**	**Biomarker of GLY Dys**	**Footprint of ischemia**	**Biomarker of SVD/stroke**

Ten Major TEM Remodeling Changes Associated with Brain Endothelial Cell (BEC) Activation

1. BEC thickening with hypolucency that may be due to increased transcytosis in increased permeability.
2. BEC endothelial plasma membrane ruffling.
3. BEC plasma membrane microparticles/microvesicles and extracellular exosome formation.
4. BEC increased aberrant mitochondria that are leaky and leak mtROS (superoxide) and increase BEC redox stress.
5. BEC increased endoplasmic reticulum (ER) with swelling and widening of ER with ER stress.
6. BEC increased transcytosis associated with inflammatory LPS induced vascular inflammation.
7. BEC attenuation and/or loss of the ecGCx.
8. BEC basement membrane thickening with vesiculation and vacuolation.
9. BEC stiffening associated with contraction and loss of elongation with shortening of BECs.
10. BEC activation association with adherence of leukocytes, red blood cells and platelets making them proinflammatory, proatherosclerotic - proarteriolosclerotic, and prothrombotic.

Pericyte and Brain Endothelial Cell Protein Interactions and Interdependent Biomarkers and Signaling Proteins

Protein	Pericyte	Endothelial cell
VEGF A ***(VEGF B)*** synthesized and secreted by BEC	+	–
PDGF-B	–	+
PDGF-B (R)	+	–
eNOS	–	+
ET-1	–	+
Basement Membrane (Type iv collagen, laminin, and glycosaminoglycans)	+	+
Markers		
NG2 proteoglycan	+	–
α -SMA	+	–
mAb (3G5)- defined ganglioside cell surface marker	+	–
vWf	–	+
LDL-C R	–	+