Adjourning Alzheimer's

Synopsis - The Elusive Origins Of Alzheimer's (Day 29)

We've covered **a lot of material** in this first month. It's time to do a recap!

(1) A Brief History Of Alzheimer's

Throughout human history, dementia has been regarded as an **inevitable feature of aging**, a fact that has hampered serious attempts to treat it. Amazingly, it was not until 1907 that neuropathologists Alois Alzheimer and Oskar Fischer clearly described the **pathological plaques, tangles, and neuron loss** of Alzheimer's. Even more amazingly, it was not until 1976 that neurologist Robert Katzman extended the definition of Alzheimer's to include all people with the disorder, regardless of age.

(2) Neuron Loss

The event most directly responsible for the clinical dementia of Alzheimer's is **neuron loss**. This neuron loss is **selective** for the hippocampus, entorhinal cortex, and temporal and parietal lobes of the cerebral cortex; other brain structures are relatively unaffected. Rather than see it as an inevitable feature of aging; it's better to think of Alzheimer's as a long pathological process that extends into old age.

(3) Excess Amyloid Beta

Aside from neuron loss, one of the most obvious pathological hallmarks of Alzheimer's is **excess amyloid beta** (Aβ), resulting in extracellular Aβ plaques. The **amyloid cascade hypothesis** posits that excess Aβ is the main culprit driving neuron loss. Unfortunately, the strongest evidence for this hypothesis is based on in vitro studies, animal studies, and humans with rare genetic alterations such as familial Alzheimer's and Down's syndrome, rather than the vast majority of people with the sporadic form of Alzheimer's. Moreover, excess Aβ and neuron loss do not correlate well; the Aβ plaques appear in the wrong place at the wrong time.

(4) Tau Accumulation

Aside from neuron loss and Aβ plaques, another obvious pathological hallmark of Alzheimer's is **tau accumulation**, which leads to pretangles and neurofibrillary tangles. Neuropathologist Heiko Braak showed that compared to excess Aβ, the pattern of tau accumulation correlates much better with the pattern of neuron loss; moreover, tau starts to accumulate 30 years before excess Aβ appears. These facts support the **tau hypothesis** - tau accumulation leads to pretangles and tangles that interfere with neuron function, followed by neuron loss. However, a major weakness of this hypothesis is that tau accumulation alone is not lethal; neurons with tau accumulation may survive for decades, and by 70 years of age the majority of people have appreciable tau accumulation, but no neuron loss.

(5) Mitochondria Dysfunction

Neurons must be able to generate large amounts of energy at any time by maintaining a healthy pool of mitochondria. In Alzheimer's, there is **mitochondria dysfunction** in the form of altered population dynamics, structure, and function, all of which culminates in energy failure for the neurons. The **mitochondria cascade hypothesis** posits that aging somehow triggers the mitochondria dysfunction, followed by energy failure and neuron loss. Yet since cognitively normal elderly people do not necessarily show much evidence of mitochondria dysfunction, it is not an inevitable feature of aging, and since many other cells in Alzheimer's show mitochondria dysfunction but do not die, the dysfunction is unlikely to be the sole culprit driving Alzheimer's.

(6) Microtubule Disassembly

The track-like **microtubules** link tau accumulation with mitochondria dysfunction; tau proteins regulate microtubule assembly and disassembly, whereas mitochondria use them as a means of transport. The **microtubule hypothesis** posits that an initial build-up of hyperphosphorylated tau leads to excessive microtubule disassembly, followed by tau release (culminating in tau accumulation) and impaired mitochondria movement (culminating in mitochondria dysfunction). This hypothesis is consistent with the high concentration of hyperphosphorylated tau, early axon abnormalities, and dearth of microtubules observed in Alzheimer's. Yet it does not explain where hyperphosphorylated tau comes from, nor does it explain the selective neuron loss for the hippocampus, entorhinal cortex, and temporal and parietal lobes of the cerebral cortex seen in Alzheimer's.

(7) Impaired Brain Insulin Signalling

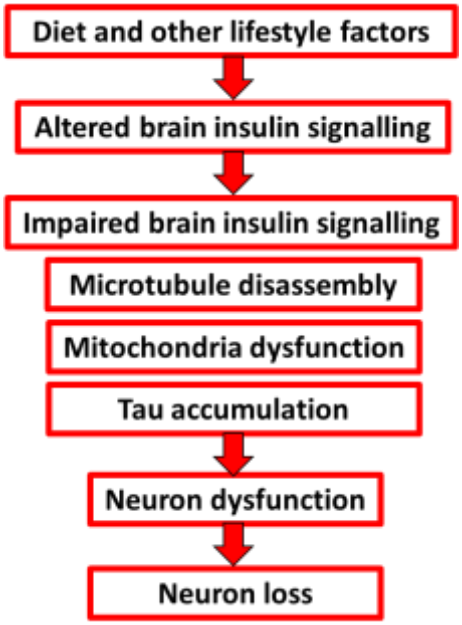
Ordinarily, the main fuel for neurons and glia is glucose; entry of glucose into brain cells is regulated by insulin, which binds to insulin receptors on the cell membrane. Neuropathologist Suzanne De la Monte has argued that since there is both a brain insulin deficiency as well as brain insulin resistance in Alzheimer's, it is a form of **impaired brain insulin signalling** or "type 3" diabetes. These facts support the **impaired brain insulin signalling hypothesis** - that chronic overuse leads to compromised brain glucose metabolism, microtubule disassembly, tau accumulation, mitochondria dysfunction, and neuron loss. The hypothesis explains the build-up of hyperphosphorylated tau (as low glucose levels in the cell trigger hyperphosphorylated tau) and selective neuron loss for the hippocampus and other affected brain structures (as they rely much more on insulin than other brain structures).

We have presented multiple hypotheses regarding the **obscure origins** of Alzheimer's. There are two problems with our approach. First, the list we have presented is **not necessarily comprehensive**; we have presented major factors, but there may be others that influence the progression of Alzheimer's. Second, we have presented each hypothesis in a **stand-alone fashion**. However, it is difficult to be definitive about one feature "causing" another; more likely, all the pathological features we have discussed affect each other in a complex fashion, and putting them all together results in something more convoluted than what any single hypothesis posits.

Nonetheless, out of all the features of Alzheimer's that we have discussed, it is hard to ignore the fact that **brain insulin signalling features prominently**, and appears to influence all the others. Brain

insulin signalling must be chronically altered before it is chronically impaired, and since insulin signalling primarily responds to dietary and lifestyle factors, it is not unreasonable to suspect that a person's **diet and lifestyle** may play a powerful role in the genesis of Alzheimer's. If we work hard to improve brain insulin signalling, then maybe we can influence the microtubules, mitochondria, tau, and neuron loss as well.

That being said, let's cluster all these hypotheses into one cohesive **chain of pathological events that is Alzheimer's**; since they slowly develop over years or decades, we will group impaired brain insulin signalling, microtubule disassembly, mitochondria dysfunction, and tau accumulation together:



The long chain of pathological events that is Alzheimer's.

This is our framework for the **Alzheimer's pathological process**; clearly, it is not a single event but a continuum of events, the origin of which is dominated by dietary and lifestyle factors (as opposed to aging or genetics), the end of which is marked by neuron loss manifesting as cognitive impairment. We shall return to the role of dietary and lifestyle factors in Alzheimer's again in several weeks, but for now, let us turn our attention towards the road to diagnosing Alzheimer's.

Matt (Neurologist, Waikato Hospital).