Links Between the Oral Microbiome, Aging and Alzheimer's Disease

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The human microbiome accounts for roughly 1-3% of body mass with 10 bacteria for every human cell, and bacterial load is likely to increase with age.

Bacteria are found in greatest numbers and variety in the mouth, the gut, and on the skin. These specific bacteria form biofilms: a complex ecosystem of different species of bacteria forming a symbiotic whole.

Commensal oral and gut bacteria metabolize components of the food we eat and release compounds which can be absorbed into the bloodstream. Hence, they contribute, with good and bad effect, to the chemicals circulating around our bodies.

An important feature of the alimentary tract is the immune tolerance afforded to the bacteria that reside there. This is necessary because the immune system must ignore foodstuffs, which presents a potential hazard if any of our "commensals" migrate from their normal site of residence. There is increasing evidence revealing that they do just that. Also increasing evidence that the Blood-Brain barrier and placenta fail to provide comprehensive protection.

The composition of the microbiome is influenced more by environmental and social factors than the host's genetic background as illustrated by a study of identical twins. This is particularly relevant in the context of data for identical twin pairs linking Alzheimer’s disease (AD) to oral bacteria.

Examples of the Microbiome Linked to Disease:

Red meat consumption has been long implicated as a risk factor for atherosclerosis even when the meat consumed was lean and low in cholesterol. Trimethylamine-N-oxide (TMAO) forms part of the cascade to atherosclerotic plaque development and raised levels in blood act as a biomarker for atherosclerosis risk.

Studies show that individuals with diets rich in red meat produce more of a metabolite known as L-carnitine which indicates how diet influences the gut bacteria. Vegans and vegetarians produce less TMAO suggesting that people with low red meat diet have fewer of the specific bacteria required for TMAO production.

This is one example of how diet influences the composition of the microbiome and how components of the commensal microbiome contribute to developing a disease such as atherosclerosis

Type II Diabetes and the Microbiome:

In developing countries such as India and Brazil where obesity is less prevalent, treatment for periodontitis improved glycemic control. However, in the US, a large trial providing periodontal treatment to Type II diabetic patients show no improvements in glycemic control. (Worth noting: the US trial did not use systemic antibiotics and no information was available regarding the BMI of patients). It therefore remains possible that in the US population there may be a greater contribution to type II diabetes by bacteria further down the gastrointestinal tract.

Obesity is an established risk factor for type II diabetes and has long been linked to the overgrowth of certain gut bacteria. A recent study has explored the differences between the gut microbiomes of pairs of identical and fraternal human twins discordant for obesity. Revealing, astonishingly, that obesity was transmissible.

Gut bacteria cultured from each twin were fed to mice reared in a sterile environment, with no developed microbiome of their own. The mice receiving bacteria from the obese twins ("fat" bacteria), developed obesity and those receiving bacteria form the thin twins ("thin" bacteria) remained normal weight, even though all mice were fed the same amount of food.

The conclusion from these studies was that it is the combination of having a predominantly "thin" flora and being fed a healthy diet is important for maintaining a normal weight. A poor diet, lacking fruits and vegetables, will likely result in the "thin" bacteria being out-competed by any available "fat" bacteria

Exploring the Links Between Alzheimer's Disease and Oral Bacteria:

Dimentia affects one in 14 people over 65 years of age and one in six people over 80 years of age in the UK. Alzheimer's Disease (AD) symptoms frequently begin with loss of ability to form new memories, leading to confusion.

One of the more surprising correlations chronicling the life and medical histories of twins was that of dementia with tooth-loss in early to mid-life. One of the three potentially modifiable risk factors, tooth-loss before age 35, poor education, and short adult stature, only tooth loss was statistically significant in the identical twins discordant for dementia. Bearing in mind identical twins that live apart are unlikely to share the same oral microbiome, this emphasizes a potential link between oral hygiene and dementia risk.

Assuming that tooth loss provides a rough indicator for poor oral hygiene, this link was further corroborated by an eighteen-year longitudinal study from the US. Dentate individuals who did not brush their teeth daily were reported to have a 22-65% greater

risk of developing dementia compared with those who brushed their teeth three times daily.

Experimental Evidence linking Oral Bacteria to Alzheimer's Disease:

Evidence of bacteria found in brains:

In 2011, Miklossy published a review indicating that oral bacteria were present at ~7-fold higher density and far greater variety in Alzheimer's Disease brains compared to cognitively normal controls.

Among the AD patients examined, the most prevalent class of bacteria were oral spirochetes that are obligate anaerobes

PCR also identified Treponema in 14 out of 16 AD brains compared with 4 of 18 controls with more species represented in AD.

Riviere and colleagues also examined trigeminal ganglia for bacterial infiltration by PCR. Treponema were detected in all subjects, however only samples from AD patients had Treponema maltophilum.

These findings suggest that certain bacterial phyla, in this case oral anaerobes, are more closely associated with AD, since they were not as heavily represented in the non-AD samples.

Whether oral bacteria themselves or endotoxins (e.g. LPS) released by them gain access to the brain, the net result is likely to be microglial activation; which is a well-recognized feature of AD and results in the increased production of pro-inflammatory cytokines such as TNF-alpha and IL1-beta.

Potential Route of Entry for Oral Bacteria to the Brain in Alzheimer's Disease:

Many nerves lead from the oronasal cavity directly to the brain; including the trigeminal and olfactory. The trigeminal nerve has been shown to harbor Treponema and may act as a route of entry for oral bacteria into the brain in AD.

Another potential route is the olfactory nerve, particularly in the context of hyposmia or anosmia as a heralding symptom for many neurodegenerative diseases, including AD.

Take Home Message:

Our microbiome influences our health and ultimately how well we age. There is evidence linking the oral bacteria to Alzheimer's disease (AD) in the context of aging. Aging may favor the proliferation of anaerobes in the mouth eliciting a TNF-alpha response from the oral epithelium - compromising the integrity of the Blood-Brain Barrier. This theory hypothesizes that bacteria can then enter the brain through the depleted, or less active BBB, allowing these bacteria to spread and create some sort of chronic inflammatory response (such as in cases of atherosclerosis). It is these inflammatory responses which has been long associated with AD.

References:

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