



Alzheimer's disease might depend on enabling pathogens which do not necessarily cross the blood-brain barrier

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ABSTRACT

The development of Alzheimer's Disease (AD) might reflect, in its acquired aspects, a cooperative pathogenesis whereby infectious enablers which do not necessarily cross the blood-brain barrier augment the invasive properties of a less virulent organism, thus enabling it to infect the brain. An example interaction is described which involves *Chlamydia* species, *Human papillomavirus* (HPV), microbiota, and yeast, where yeast is a pathogen of low virulence which crosses the blood-brain barrier. The cooperative pathogenesis begins at the mucosal epithelium. Infection by *Chlamydia*, HPV, or dysbiosis of commensal bacteria disrupts the integrity of the mucosal epithelium, thereby allowing colonizing yeast to penetrate the epithelial barrier and enter into the bloodstream. *Chlamydia* and enabling commensals promote insulin resistance, which provides yeast with glucose and also sets the stage for accumulation of amyloid beta protein (ABP). Meanwhile, HPV-induced and hyperglycemia-induced immunological changes enable the spread of newly invasive yeast to the brain, where the release of inflammatory cytokines in response to yeast promotes production of ABP. *Chlamydia* also cross reacts with *Candida* species, which may stimulate further brain inflammation in response to *Candida* and may augment production of ABP thereby. The yeast's less virulent origins, coupled with immune modulation by enablers, might explain why AD as a model of infectious encephalitis is always slow and insidious rather than occasionally febrile, accompanied by seizures, or marked by signs of meningeal inflammation.

Introduction

Background

One of the hallmarks of the Alzheimer's Disease (AD) brain is the deposition of extracellular deposits of amyloid as amyloid senile plaques. The main component of amyloid plaques is amyloid beta protein (ABP), a neurotoxic pro-inflammatory compound with antimicrobial properties and antimycotic activity [1]. Amyloid plaque formation leads to brain inflammation, with release of reactive oxygen species which damage DNA, a further risk factor for AD. Amyloid plaque formation also leads to excessive phosphorylation of tau protein, with consequent damage to the microtubular structures of the neuron [2].

Though the reasons for the overproduction of amyloid beta protein (ABP) are not well understood, inflammation of the central nervous system is thought to play an important role in the pathophysiology of AD [2]. A potential infectious or inflammatory etiology for AD is supported by the observation that pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), interferon gamma (IFN-gamma), and various interleukins are elevated in the brains of AD patients [3]. Some of these pro-inflammatory cytokines act to increase the risk for development of senile plaques: for example, TNF-alpha stimulates cleavage of amyloid precursor protein (APP) into ABP [4,5]. By stimulating increased production of ABP, TNF alpha promotes the

development of senile plaques.

Proposed infectious etiologies for AD

There is compelling evidence to support the potential involvement of infectious pathogens in at least some aspects of AD. Pathogens with strong evidence to support their association with AD include *Human herpesvirus-6* (HHV-6), *Human herpesvirus-7* (HHV-7), fungi, and *Porphyromonas gingivalis*. All are pathogens with tropisms for the central nervous system. HHV-6 and HHV-7 are present in the brains of patients without AD, but HHV-6 and HHV-7 viral DNA is higher in patients with AD. Also, HHV6A has been associated with induction of APPBP2 and APBB2, proteins which promote cleavage of APP to ABP [6].

The evidence for involvement of fungi in AD is perhaps even more compelling than for HHV-6 or HHV-7: in brains of patients with AD, immunohistochemical staining of brain tissue using anti-*Candida glabrata* antibodies revealed mycosis in brain regions associated with AD, including the external frontal cortex, the cerebellar hemisphere, the entorhinal cortex/hippocampus, and the choroid plexus. In brains of patients without AD, immunohistochemical staining revealed no mycosis at all [7].

And most recently, the bacteria *Porphyromonas gingivalis*, a bacteria associated with periodontitis, was identified in the brains of AD patients and was shown to be a significant inducer of AD pathology,

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including increased ABP and increased tau pathology [8].

Nevertheless, important questions remain. If yeast infections, herpes viral infections, or infections by gingival bacteria are causal events for development of AD, then it must be explained why AD does not follow a typical course for herpes viral, fungal, or bacterial encephalitis or meningoencephalitis. In AD there are no seizures, no headaches, no fever, no obtunding fatigue, and no signs of meningeal irritation: symptoms which might be expected in at least some cases of AD were AD to follow the model of a more typical acute or virulent encephalitis. Also, the very pathogens which appear to be most closely associated with AD—HHV-6, HHV-7, yeast, and oral bacterial pathogens—are pathogens which exhibit little systemic virulence in most people. Which factors distinguish AD from a classic infectious encephalitis, and which factors might contribute to newly augmented virulence in a formerly commensal organism or in a microbe of relatively low virulence?

A potential role for *Chlamydia pneumoniae*

A discussion of the topic of AD-related pathogens would be incomplete without mention of *Chlamydia pneumoniae*, a pathogen which has been identified and localized in the brains of patients with AD [9]. *Chlamydia pneumoniae* has been associated with other diseases of the central nervous system in addition to AD, including multiple sclerosis and schizophrenia [10,11]. It remains unclear how *Chlamydia pneumoniae* might contribute to the specific pathogenesis of AD.

Chlamydia pneumoniae is capable of infecting macrophages, monocytes, and lymphocytes [12], and one important action of *Chlamydia pneumoniae* is to increase Th2 activation [13]. Indeed, in experimental allergic encephalitis, a model for multiple sclerosis which is characterized by activation of both Th1 and Th2 pathways, the presence of *Chlamydia pneumoniae* worsens the destructive inflammatory process [14,15]. Perhaps brain infection by *Chlamydia pneumoniae* plays a similar role in AD, worsening the inflammatory process of a second organism or causative factor which is already present within the brain.

Occurrences of overt *Chlamydia pneumoniae* encephalitis and meningoencephalitis (where *Chlamydia pneumoniae* is identified as the causative organism) are rare, even in the elderly – they are much rarer than fungal, bacterial, or viral causes of encephalitis [16]. Therefore, both the epidemiology of *Chlamydia pneumoniae* encephalitis and the finding that *Chlamydia pneumoniae* is involved in a variety of central nervous system diseases argue against a role for *Chlamydia pneumoniae* as the single causative organism for AD. It is much more likely that *Chlamydia pneumoniae* exerts its role as an augments of inflammation. Since infection by *Chlamydia pneumoniae* stimulates inflammation not only locally but throughout the body [17], *Chlamydia pneumoniae* might not need to be present within the brain in order to contribute to the course of AD.

Hypothesis

A dominant strategy in the search for potential Alzheimer's Disease (AD)-related pathogens has been to focus on pathogens which exhibit tropism for the central nervous system. Indeed, it seems clear that, in order to affect the brain directly, a pathogen must be able to enter the brain. But what if the pathogenesis of AD – beginning with invasion and ending with senile plaques – were less like a dart and more like a team or a relay? AD could be a manifestation of a cooperative pathogenesis whereby pathogenic microbes outside of the brain augment the virulence and invasive properties of a normally less virulent species, thus enabling it to establish brain infection. Herein is a proposed example of a cooperative process involving *Chlamydia* species, *Human papillomavirus* (HPV), gut and urinary microbiota, and *Candida* species, in which *Chlamydia* and HPV are enabling pathogens which do not need to cross the blood–brain barrier, and *Candida* “carries the baton” into the brain. In this example, *Chlamydia* species, HPV, and dysbiotic commensals 1 – facilitate the entry of yeast into the systemic circulation, 2 – manipulate

the host metabolism to better support the growth of yeast, 3 – reduce granulocyte and other immune interference with hematogenous spread of yeast, and 4 – augment brain inflammation in response to yeast. Metabolic changes and increased inflammation result in increased accumulation of ABP with reduced ABP clearance: a situation which is a set-up for the formation of senile plaques. Meanwhile, the fact of the yeast's less virulent origins, coupled with the immune modulation of enabling organisms, might explain why the development of AD as a model of infectious encephalitis is always slow and insidious rather than febrile, accompanied by seizures, or marked by signs of meningeal inflammation.

Evaluation of the hypothesis

Selection of proposed enablers

The possibility exists for synergistic interactions between species of yeast and a multitude of pathogenic organisms outside of the brain, but not all of these interactions are relevant to the development of AD. Therefore, for the purposes of this discussion, selection of proposed enabling pathogens was accomplished on the basis of five criteria: 1 – the proposed enabler must be common; 2 – the proposed enabler must share a tissue tropism (outside of the brain) with potentially relevant *Candida* species; 3 – the proposed enabler must be capable of augmenting the virulence or invasiveness of *Candida* in some way; 4 – the enabler must be able to exert its effect from outside of the brain 5 – the proposed enabler must be chronic or recurrent.

Herpesviruses and *Porphyromonas gingivalis* share tissue tropisms with *Candida* species, and there is some in vitro evidence to support the possibility that HSV-1 may support the growth of *Candida albicans* [9]. It is quite possible that interactions between these organisms within the brain increases the risk for AD. However, the focus of this hypothesis is on enabling organisms which, despite their non-brain location, might be capable of potentiating the virulence and invasive properties of *Candida*. It is suspected that herpesviruses and *Porphyromonas gingivalis* might require brain invasion in order to augment the virulence of other pathogens. Therefore, these pathogens have not been included in the list of proposed enablers below.

Epidemiology of proposed enablers

Epidemiology of *Chlamydia*

Chlamydia species are important pathogens in the elderly population. *Chlamydia pneumoniae* has been implicated as an important cause of nursing home outbreaks of community acquired pneumonia [18–21]. Infection by *Chlamydia pneumoniae* may be either acute or chronic, and many mild or asymptomatic *Chlamydia* infections go undetected. In a Finnish epidemiological study from 2005, 46–87% of individuals exhibited IgG titers to *Chlamydia pneumoniae*, and 27–57% of individuals exhibited IgA titers to *Chlamydia pneumoniae*. The prevalence of IgG and IgA antibodies to *Chlamydia pneumoniae* were significantly higher in individuals of older age (40 years and above) than in individuals of younger age (under 40 years) [22,23].

According to data reported by the CDC for 2016, infection by *Chlamydia trachomatis* is on the rise in all age groups, including in the older adult cohort. While reported cases of *Chlamydia trachomatis* infection are less common among older adults, most *Chlamydia* infections are asymptomatic. Also, physicians are less likely to screen for *Chlamydia trachomatis* in their older patients [24].

For both *Chlamydia pneumoniae* and *Chlamydia trachomatis*, treatment failure is a significant problem. In one study from 2005, 13% of women treated for *Chlamydia trachomatis* using standard antibiotic protocols exhibited persistent or recurrent infection with *Chlamydia trachomatis* [25]. A review from 2012 reported treatment failure rates for *Chlamydia trachomatis* ranging between 5 and 23% [26]. Exposure of *Chlamydia* to penicillin may affect subsequent efficacy of treatment

with macrolides: in one study, exposure of chlamydia trachomatis to penicillin render the bacteria phenotypically resistant to azithromycin [27]. Persistence of *Chlamydia pneumoniae* has also been described: in a continuous model of *Chlamydia pneumoniae* infection, macrolides were unable to eradicate the organism [28].

Epidemiology of HPV

Human papillomavirus is the most common sexually transmitted infection in the United States [29] and an important cause of morbidity worldwide. Prevalence of genital infection with any type of HPV type was 42.5% among United States adults aged 18–59 years during 2013–2014. HPV is often characterized as a disease of younger adults during fertile and childbearing years, but it is also common in older adults. In a retrospective study from 2008, nearly 1 in 16 US women between the ages of 57–85 were found to have documented high risk HPV [30]. In a Swedish study, the prevalence of HPV in women between the ages of 60–89 years was 4.1% [31]. These studies most likely underestimate the prevalence for HPV, since most older individuals are probably not screened for HPV. There is also evidence to indicate that the incidence of HPV infection in older adults may be growing: for example, HPV-associated oropharyngeal cancer is on the rise in patients aged 70 and older [32].

There is some evidence to suggest that HPV can establish latency in the basal epithelial stem cell pool, with periodic induction of reactivation as stem cells divide and differentiate. Latency of HPV has been established in rabbits, and several human studies suggest that latency may be an aspect of human HPV infection, as well. Women observed to have cleared a specific HPV genotype during the study period were evaluated for recurrence of HPV. In a significant number of women, recurrence of HPV was with the same genotype rather than with other genotypes, which suggests the possibility of latency with subsequent reactivation of infection [33,34]. In the elderly, reactivation of HPV might coincide with the age-related immunosuppression commonly found in this population.

Commensals

Several commensals are worth mentioning in an epidemiological discussion of potential enablers for invasive *Candidal* infection and AD. *Gemella* species is found in greater number in the urinary microbiota of men with sexually transmitted infections (*Neisseria gonorrhoea* or *Chlamydia trachomatis*) than in men without [35]. *Gemella* is one of the species which has been found to have a specific association with AD [36].

Sneathia species are found in greater number in the urinary microbiota of men with sexually transmitted infections (*Neisseria gonorrhoea* or *Chlamydia trachomatis*) than in men without [35]. In women, *Sneathia* is an important contributor to the pathogenesis of bacterial vaginosis, a condition which has been identified as a risk factor for infection by *Chlamydia trachomatis* [37,38].

Methanobrevibacter smithii is an archaeobacteria which is frequently found along with candida species in the gut microbiota [39]. *M. Smithii* promotes weight gain and the development of insulin resistance, factors which provide a rich glucose environment for candida species [40]. The presence of *Candida* in the gut microbiota also promotes the growth of *Prevotella* [39]. While *Prevotella* has not yet been demonstrated to promote weight gain, its presence tends to exclude *Bacteroides*, a resident pathogen which appears to counter weight gain and other aspects of the metabolic syndrome [41–43].

Tissue tropisms for proposed enablers

Chlamydia species and HPV share a number of external tissue tropisms with *Candida* species. HPV and *Candida* species share tissue tropisms for the male and female external genitalia, the vagina and cervix, and the oral cavity. *Chlamydia trachomatis* and *Candida* species share tissue tropisms for the urethra and for vagina/cervix. The affinity of *Chlamydia pneumoniae* for the upper and lower respiratory tract is not

the same as that of *Candida*, but it intersects with the affinity of *Candida* for the mouth, throat, and esophagus.

Commensals such as *Sneathia* and *Gemella* share the candidal tropism for the genitourinary tract [35], whereas *M. smithii* and *Prevotella* are associated with resident candida species in the gut [39,41].

Crossing the mucosal epithelial barrier

For a *Candida* species to become invasive, the yeast must be able to penetrate the epithelial border and must also be able to produce functional hyphae. Organisms such as *Chlamydia*, HPV, and various commensals facilitate the invasiveness of *Candida* by interfering with normal epithelial integrity, by causing direct damage to epithelial cells, or by altering host immunity and host metabolism in ways which facilitate formation of hyphae [43]. Through these mechanisms, *Chlamydia*, HPV, and dysbiotic commensals support the invasive spread of yeast.

Symbiotic interactions between enablers

The cooperative process between candida and the other enabling organisms begins at the mucosal epithelium, where the growth of local yeast supports the growth of dysbiotic commensals such as *Sneathia* and *Methanobrevibacter smithii*. *Sneathia* species can be commensal, but they are also among the species capable of producing bacterial vaginosis. Bacterial vaginosis, in turn, is a risk factor for infection by *Chlamydia trachomatis*. *Methanobrevibacter smithii*, a commensal archaeobacteria which promotes obesity and insulin resistance, is described in a later section.

Chlamydia species and HPV are also synergistic for one another: HPV induces shifts to the Th2 and Th17 pathways with increased formation of IL-13 and IL-17 [44–46]), and *Chlamydia* species thrive in the presence of IL-13 [47]. In turn, the presence of *Chlamydia trachomatis* increases the risk for infection by high risk strains of HPV [48]. The same relationship might also hold between chlamydia pneumoniae and high risk HPV in the oral cavity.

Disruptors of epithelial integrity within the genitourinary tract

In the genitourinary tract, chlamydia trachomatis and HPV work alone or in concert to damage epithelial cells and to disrupt the integrity of the mucosal epithelium, thereby facilitating the invasive capacity of candida. In the urogenital tract, low risk HPV produces condylomata which are prone to bleeding and tissue breakdown. High risk HPV may result in cervical interstitial neoplasia (CIN), with tissue damage to the cervical epithelium and loss of cellular orientation, changes which can alter the epithelial barrier.

Chlamydia trachomatis, for its part, produces inflammation both at the cervix and urethra, with purulent inflammatory discharge. These changes, too, can disrupt the epithelial barrier, thereby partially removing obstruction to invasion by local candida species.

Disruptors of epithelial integrity within the oral cavity and upper respiratory tract

Candidal colonization of the oral cavity increases with advanced age, and here, too, it interacts with HPV: epidemiological data indicate that HPV-induced oral carcinoma is on the rise in the elderly population [32]. As with the cervical epithelium, in the oral cavity, active infection of HPV or reactivation of latent HPV induces malignant transformation of epithelium, which can produce defects in the functioning of the epithelial barrier. These defects would then be available for exploitation by the resident *Candida* flora.

Candidal flora also interacts with *Chlamydia pneumoniae*: as the respiratory tree intersects with candida inhabited regions such as the oral cavity, throat, and larynx, *Chlamydia pneumoniae*-induced inflammation can create defects in the epithelial lining which might then be exploited by resident candida flora.

Disruptors of epithelial integrity within the gut

Dysbiosis of gut microbiota can lead to inflammation of the gut lining and in extreme cases may predispose to inflammatory bowel disease (IBD) [49]. Even in “milder” cases, gut dysbiosis predisposes to disruption of the intestinal epithelial lining, with widened opportunities for spread of candida. *Gemella* and *Prevotella* species (see above) are positively associated with IBD, whereas *M. Smithii* appears to have an inverse relationship with IBD [50].

Metabolic factors

Metabolic factors which promote the growth of candida species

Many of the same pathogens which facilitate invasion of candida species also increase the risk for aspects of the metabolic syndrome, a metabolic state which supports the growth and defense needs of candida. Infection by *Chlamydia* species or colonization by *M. smithii* and associated gut commensals increase the risk for weight gain, hypercholesterolemia, and insulin resistance [49–52].

The insulin resistant state is a boon for yeast. For *Candida albicans*, elevated glucose serves as both a virulence factor and a protective factor. Exposure of *Candida albicans* to glucose triggers hyphal morphogenesis, which is associated with an increase in virulence of the phenotype. Exposure to glucose also induces the transcription of genes involved in oxidative stress adaptation, which renders the yeast more resistant to toxic and phagocytic stresses [53]. It is likely that other *Candida* species exhibit responses to glucose which are similar to that of *Candida albicans*. For example, in animal models, diabetes mellitus increases the virulence of vaginal *Candida glabrata* [54].

In addition to the above, diabetic nephropathy supports the growth of *Candida* species through its suppression of uromodulin [55], an immune peptide which is important in the host defense against yeast. Uromodulin binds to hyphae and suppresses the growth of yeast [56]. Uromodulin also increases production of cytokines such as IL-6 and TNF alpha, cytokines which combat the growth of yeast [57,58]. Under conditions of diabetic nephropathy, however, production of uromodulin is suppressed, which increases the ability of *Candida* species to thrive and grow, both within the kidney and also within the systemic circulation.

In sum, by predisposing to obesity, insulin resistance, and the metabolic syndrome, and by providing candida with its nutritional needs, pathogens and commensals such as *Chlamydia* species and *M. Smithii* increase the virulence and invasiveness of candida species.

Metabolic support of yeast: possible adaptive benefits for enabler pathogens

What might enabler pathogens stand to gain by manipulating the host metabolism in the direction of insulin resistance and obesity, thereby supporting the growth of yeast? For commensals within the gut and urinary system, the symbiotic connection between commensal bacteria and yeast might be nutritional. As *Candida* species release carbohydrates and/or sugars into the local environment, these carbohydrates and sugars become available for metabolism and fermentation by associated commensal bacteria. For those commensal organisms which feed off of the carbohydrates released from yeast, supporting the growth of *Candida* would be expected to confer adaptive benefits.

Chlamydia species cannot metabolize sugars released by yeast, as they lack the cellular machinery required for phosphorylation of sugars. Therefore, a symbiotic relationship between *Chlamydia* and yeast could not be based on the carbohydrate needs of *Chlamydia*. However, a symbiotic relationship might be based on essential amino acids released from yeast. In addition to sugars, yeasts manufacture tryptophan [59,60], sometimes to excess. Tryptophan is an essential amino acid for chlamydia [61], and furthermore, low levels of cervicovaginal tryptophan have been associated with increased clearance of *Chlamydia trachomatis* from the female genital tract [62]. By increasing local tryptophan, yeast might increase survival and virulence of chlamydia.

Alternatively, by supporting the growth of yeast, *Chlamydia* might

acquire adaptive benefits related to attachment to host tissues. Under nutritional stress conditions, such as when glucose is scarce, *Candida albicans* increasingly incorporates chitin into its cell walls [63]. Chitin can be metabolized by exochitinase-producing resident flora into chitobiose [64], a compound which interferes with the ability of chlamydia to bind to host cells. It could be of significant benefit to *Chlamydia* to limit production of both chitin and chitobiose within the local environment [65]. By keeping resident yeasts “well fed,” thereby reducing chitin incorporation into yeast cell walls, *Chlamydia* might be preserving its own virulence and survival.

It is also possible that *Chlamydia* manipulates the host metabolism for reasons which have little or nothing to do with candida. In that case, *Candida* is merely an unintended beneficiary of metabolic changes induced by *Chlamydia* species.

Metabolic factors which promote the accumulation of excessive amounts of ABP

Insulin resistance is a known risk factor for the development of AD. Diabetes mellitus confers a 56% increase in risk for the development of Alzheimer’s dementia [66], and even pre-diabetes has been implicated as a potential risk factor for AD [67]. Other metabolic risk factors for AD include hypertension, obesity, and dyslipidemia [68]. At least some of these metabolic imbalances exert their effect by promoting the accumulation of ABP.

Diabetes mellitus and obesity interfere with clearance of ABP in several ways. First, a state of insulin intolerance or insulin deficiency interferes with the low density lipoprotein (LDL)-receptor-related protein (LRP) pathway, an insulin-dependent pathway which is involved in clearance of ABP [69,70]. The LRP pathway sequesters and remove soluble amyloid beta-protein from brain and other tissues, rendering them less available for plaque formation. Higher levels of LRP are protective against AD. After LRP1 has cleared ABP from the local neural environment, insulin stimulates recycling of LRP1 to the plasma membrane. The recycling of LRP1 back to the plasma membrane renders the LRP1 available for another round of ABP clearance. Insulin resistance reduces the rate of recycling of LRP1, which renders LRP less available for ABP clearance.

Increasing adiposity also plays a role in the accumulation of ABP. First, obesity predisposes to a pro-inflammatory state which is characterized by increases in pro-inflammatory cytokines such as TNF alpha [71]. As mentioned previously, TNF alpha cleaves APP into ABP fragments, thereby increasing production of ABP [4]. Second, increasing adiposity reduces the effectiveness of the LRP pathway: differentiation of 3T3 cells into adipocytes is associated with a reduced LRP-1 recycling rate, which reduces the availability of LRP for elimination of amyloid beta protein [71].

Regarding adiposity as a risk factor for AD, it has been observed that elevated BMI during midlife corresponds to an increased risk for AD, whereas elevated BMI at older ages is associated with a decreased risk for AD [72]. The reasons for this biphasic relationship with BMI remain unclear. It may be that adiposity is a risk factor for AD only during the early stages of development of AD, but that as AD becomes more advanced, with increasing disruption of microtubules and increasing interference of synapses by hyperphosphorylated tau, the disease comes to resemble a prion-induced disease state which is independent of inflammatory or metabolic factors [73]. Alternatively, since lower BMI is associated with higher mortality in the elderly population, it is possible that lower BMI in the elderly is a marker for a lower level of health overall [74], including a weaker immunological state. For example, the decrease in BMI associated with the onset of dementia is thought to reflect – at least in part – a nutritional decline and an overall decline in self care [75]. Surely, such a nutritional decline would be expected to hamper recovery from AD processes on multiple levels, from immune responses, to decreased ability for cell repair, to decreased energy availability for tissues throughout the body.

Immunological contributors to AD

Prevalence of AD reaches its peak in the “old old,” between 95 and 100 years of age. In this age group, AD has been estimated to affect around 30–40% of the population. Epidemiological evidence suggests that AD may not be an inevitable disease of aging, since the risk for AD appears to level off at around age 95. Beyond that point the AD prevalence actually decreases to some extent, and by age 104 or so, dementia by hippocampal sclerosis overtakes AD in prevalence [76].

The fact that AD prevalence levels off and even decrease beyond a certain very old age suggests that AD is a disease process which involves risk factors. Nevertheless, the factors which predispose an elderly individual to develop AD are incompletely understood. Not every individual who suffers from AD is insulin resistant, and among individuals with AD who have not been insulin resistant or who have not expressed metabolic risk factors for AD, not all of them are known to have genetic predispositions. It is likely that the immune system plays a crucial role in the pathogenesis of AD.

It is possible that immunological changes of aging, on their own, are sufficient to enable the pathogenesis of AD, without the contribution of additional metabolic derangements or infection-induced immunologic factors. Similarly, it is possible that the immunological changes of aging, on their own, are sufficient to enable the transformation of an otherwise minimally virulent pathogen into a much more dangerous one, without requiring the pathogenic cooperation of other species.

But if these presumptions were true, that aging alone were sufficient to enable opportunistic brain infection and AD, then why would AD prevalence decrease rather than increase in the oldest old? Why would individuals who live beyond the age of 100 carry a lower risk for AD in comparison to individuals in their mid to late 90's? Rather, these epidemiological data appear to suggest that it is not aging alone but rather a combination of aging and certain risk factors which predispose to AD. Perhaps the individuals who lack those risk factors, the ones who are most likely to live past the age of 100 years old, are also the ones who lack vulnerability to infection by organisms of lower virulence, such as *Candida* species, HHV-6, or HHV-7. These questions remain to be explored.

Immunological and other changes observed with aging

Aging affects multiple aspects of immune system function. Normal immunological alterations in the elderly include functional insufficiencies of monocytes and macrophages, decreased numbers of antigen presenting cells (such as dendritic cells), decreased numbers of naive T cells, decreased numbers of B cells, decreased antibody production, decreased T cell memory, and decreased cytokine production [77].

Given these decreases, immunological cells such as granulocytes might be expected to play an increasingly important role in immunity. In general, medications which reduce granulocyte function have been observed to adversely affect the host response to yeast [78]. In the elderly, the fact that HPV decreases both neutrophil function and chemotaxis [79] could be devastating in the context of invasive yeast.

In the oral cavity, aging leads to hyposalivation, which affects the composition of oral flora and leads to increased growth of candida species. The risk of oral candidiasis is still higher in those with dental prostheses [77]. Elsewhere in the body, as well, physiological changes may disrupt mucosal and cutaneous barrier function, with associated increased vulnerability to yeast.

Other physiological changes in the elderly which can affect the host response to disease include decreases in renal and hepatic function, as well as decreased clearance of antibiotics, corticosteroids, and other immunosuppressant medications. These changes impair immune system function and may lead to significantly increased susceptibility to a variety of pathogens, including yeast. Indeed, candida species are common in the urine of elderly patients, and in patients with disseminated candida glabrata, acute renal failure was one of the most

important predictors of mortality [77].

Immunological imbalances induced by HPV and chlamydia

The metabolic effects of HPV, chlamydia species, and commensals like *m. Smithii* have already been noted. Obesity is a proinflammatory state [71], whereas diabetes mellitus is well known to compromise the vasculature, to impair renal function, and to interfere with immunological function on multiple levels.

The section below is devoted to aspects of immunological modulation by HPV and chlamydia species which are not specifically related to the metabolic effects of these organisms.

HPV

HPV is an immunological modulator par excellence. HPV actively induces shifts to Th2 and Th17 pathways, with resultant increased production of both IL-17 and IL-13 [44,45]. In both epithelial cells and cervical tissue, HPV viral protein E7 induces elevated production of IL-17 with increased numbers of IL-17 producing cells [80]. IL-17, in turn, induces production of TNF alpha [81,82], a cytokine which stimulates cleavage of APP into ABP fragments. Women with persistent cervical HPV had higher levels of both IL-17 and TNF-alpha; it may be inferred that these women most likely also had higher levels of ABP [83].

HPV-induced increases in IL-17 are especially important in the context of yeast infection, since IL-17 increases the risk for yeast biofilm formation [84]. Formation of a biofilm is associated with increased yeast virulence. In response to invasive yeast, the host immune system would be expected to increase production of TNF alpha [81], which would promote further accumulation of ABP.

HPV-induced production of IL-13 probably plays a synergistic role in the context of *Chlamydia*, since *Chlamydia*, too, thrives in the presence of IL-13 [46,47]. This synergy goes both ways: *Chlamydia* supports the growth of oncogenic species of HPV [48]. As noted above, both of these species may induce metabolic derangements which increase the risk for AD.

Another important way in which HPV modulates immunity is via its effect on granulocyte function and chemotaxis. HPV adversely affects neutrophil function and also down regulates production of IL-8, a cytokine which plays an important role in neutrophil chemotaxis [79]. This immune modulating property of HPV might be particularly significant in the context of disseminated yeast. In mice, cyclophosphamide-induced granulocytopenia increased host production of TNF alpha while decreasing the antimicrobial activity of TNF alpha in attenuating the growth of yeast [78]. Therefore, it is possible that, in the context of HPV, the brain might produce more TNF alpha in response to yeast, thereby stimulating more production of ABP without reducing yeast in an effective manner.

Chlamydia

Infection by *Chlamydia trachomatis* has been observed to increase production of TNF-alpha [85], which, as noted above, facilitates the conversion of APP to ABP. Another factor is IL-13: both *Chlamydia trachomatis* and *Chlamydia pneumoniae* thrive in the presence of IL-13, and some chlamydia species have been found to stimulate the production of IL-13 directly [13,47,86]. This characteristic supports the synergistic growth of high risk HPV, a combination which may be a potent stimulator for TNF-alpha and production of ABP.

Furthermore, since *Chlamydia* cross reacts with *Candida* species [87], the presence of *Chlamydia* outside of the brain might be particularly effective in augmenting the candida-induced inflammatory response inside of the brain. The result of this inflammation could be further cleavage of APP into ABP fragments, with active formation of senile plaques.

Indeed, in mice with experimental allergic encephalitis, *Chlamydia pneumoniae* exacerbates this destructive inflammatory process, illustrating the ability of *Chlamydia pneumoniae* to exacerbate brain inflammation [14]. Since infection by *Chlamydia pneumoniae* stimulates

inflammation not only locally but also systemically [17], it is likely that non-brain *Chlamydia pneumoniae*, too, would be effective in stimulating brain inflammation.

In addition to the above, *Chlamydia trachomatis* supports the growth of urinary commensals such as *Gemella* species — species which exhibit increased prevalence in the context of AD [35,36]. The reasons behind associations between gemella species and AD are not known.

Consequences of the hypothesis and discussion

The cooperative model for acquired infection presented above incorporates three main elements in a triad of acquired risk factors for AD: metabolic imbalance, invasion by pathogens, and pathological changes to the microbiome.

The first element in the triad, metabolic imbalance, has been implicated as one of the most important risk factors for AD; it is, perhaps, the most important independent risk factor for AD apart from genetic predisposition.

The second element in the triad, infectious disease, is a logical inference from the evidence given the increased inflammatory markers which characterize AD, and also given the generalized immunosuppression in the elderly population. Indeed, microbial elements such as fungi and herpesviruses have already been found in the brains of patients with AD.

The third element in the triad, pathological changes to the microbiome, is increasingly recognized as a facilitator for a host of diseases. Interestingly, the presence of gemella as a commensal has been associated both with AD and also with various sexually transmitted infections, though the reasons for these correlations are not well understood. In any case, it should not come as a surprise that AD might be one of the many diseases influenced by the microbiome. All of these factors—metabolic imbalance, invasion by pathogens, and pathological changes to the microbiome—have the potential to support the development of AD.

The infectious mechanism proposed above is an example of a cooperative effort between multiple pathogenic species, of which only one of the cooperative species must cross the blood-brain barrier into the brain. In this example, yeast is the newly virulent commensal (or the pathogen of normally lower virulence), and *Chlamydia*, HPV, and dysbiotic commensals are enabling microbes which increase the virulence of yeast and enable yeast to enter into the central nervous system. The end result is increased production of ABP and impaired ABP clearance, with formation of senile plaques, hyperphosphorylation of tau, and neuronal damage.

The particular choice of enabling microbes selected above does not preclude the possibility that individuals of higher susceptibility might develop AD from infection by a single microbe, with AD developing without help from enabling organisms. Similarly, it does not preclude the possibility that, for some individuals, some but not all of the enabling microbes would be sufficient for transformation of yeast from a species of little virulence into a much more virulent species.

In a general sense, however, this model of cooperative interaction between organisms may help to explain some of the inconsistencies between the infectious model for AD and the observations which are actually seen with AD—at least in individuals who do not possess genetic predispositions or pre-existing metabolic risk factors for AD.

If AD is to be categorized as an infectious encephalitis, then it is reasonable to wonder why an individual whose immune system fights off rhinoviruses and enteroviruses year after year might develop AD. Would such an individual also be at high risk for developing other infectious encephalitides such as frank fungal, herpes, or bacterial encephalitis? Perhaps at very advanced ages the answer might be yes, but probably not at levels of incidence seen with AD. In individuals who do not possess other risk factors for AD, and in whom immunity is still reasonably functional, perhaps the necessary factor in initiating the process of AD is the physical disruption, immunological modulation,

and metabolic manipulation by enabling microbes such as chlamydia and reactivated HPV, microbes which do not necessarily cross the blood-brain barrier.

Also, if ID is a manifestation of an infectious encephalitis caused by herpesvirus, yeast, or oral bacteria, why is it observed that AD is slow and insidious in every case, without seizures, fever, headache, or meningeal signs? After all, infectious encephalitis caused by virulent herpesviruses, candida, and bacteria do sometimes exhibit these symptoms even in the oldest age groups. Perhaps the observed dearth of acute signs such as seizure and headache can be explained by the nature of the pathogen which enters the brain. If this pathogen lacks significant independent virulence, then once in the brain, it might be slow and insidious by its very nature.

It is important to note that the particular combination of microbes presented in this example is only one of a number of potential microbial combinations which might be capable of enabling an organism of relatively low virulence to infect the brain. The model presented does not preclude the possibility that enabling organisms might also be present within the brain rather than outside of it: this is self evident. What is novel herein is the concept that enabling organisms might be situated in locations which are not at all contiguous with the neuro destructive process. Even so situated, these organisms could play a critical role in enabling brain infection.

Microbes which enable the virulence of other species are potential targets for aggressive prophylaxis and early intervention in AD. For established AD, these enabling organisms could be important targets for combination therapy.

The example given above is not unreasonable. In a subset of people, at least, HPV, *Chlamydia* species, and commensal microbiota might well play irreplaceable supporting roles in the pathogenesis of AD—despite the fact that these organisms might be located outside of the brain.

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