

Perspective

Ineffective levels of transforming growth factors and their receptor account for old age being a risk factor for Alzheimer's disease

Jeffrey Fessel*

Emeritus, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

Abstract

After the midninth decade of age, the incidence rates of Alzheimer's disease (AD) and the presence of active TGF- β 1 show comparable increases. The hypothesis is proposed that the reason why advanced age is a major risk factor for AD is a progressive decrease with advancing age in the numbers of TGFR2 receptors in the brain, with the consequence of a decline in the neurotrophic efficacy of TGF- β 1 and 2 despite their already increased levels in older persons. Alternative, possible reasons are discussed but rejected because either those reasons may also affect young persons or because they cannot be validated in a clinical trial. The proposed hypothesis may be validated in persons with aMCI after raising their brain levels of TGF- β 1 and 2 by using a combination of three drugs, lithium, memantine, plus either glatiramer or venlafaxine, and then assessing their progression to AD.

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1. Introduction

Its escalating occurrence with increasing age is one of the most remarkable features of nonfamilial Alzheimer's disease (AD) but as of yet is inadequately explained. Its correct explanation would have heuristic value. Although it has been held that age is a necessary factor merely by virtue of the gradual accumulation of many deleterious events [1], this argument fails because many individuals would be exposed to all of those presumably necessary events at a much younger age than do others, creating a continuum of AD incidence between youth and a very old age; observation shows that this does not happen except for familial AD. Thus, it might be worthwhile to make an attempt to account for why spontaneous AD largely occurs after age 70.

1.1. Clues obtained from other conditions that also are seldom seen in persons less than age 50

Very few other conditions are so strongly related to old age as is AD; two of these are temporal (giant cell) arteritis and prostate cancer. Temporal arteritis seldom occurs be-

tween ages 50 and 60 and is mostly seen after age 70. Brack et al. [2] showed that temporal arteries taken from patients with this condition and implanted into humanized mice, produced large quantities of TGF- β mRNA; and it is the cells in the walls of such temporal arteries that produced TGF- β 1 [3]. With regard to prostate cancer, Steiner and Barack injected cells that overexpressed TGF- β into animals transfected with a prostate cancer cell line and saw that those animals had 50% larger tumors and 52% more lung metastases, than had control animals [4]. dos Reis et al. [5] saw significantly ($P < .002$) higher expression level of TGF- β in patients with prostate cancer having Gleason scores ≥ 7 than in those with Gleason scores < 7 .

1.2. The above reports draw attention to the possibility of TGF- β as being related to the association of Alzheimer's disease with advanced age

In the nervous system both TGF- β 1 and TGF- β 2 benefit nerves, microglia, and astrocytes, all of which participate in the pathogenesis of AD [6]. In nondemented persons, levels of TGF- β 2 rise with increasing age up to age 100+; and so also are levels of TGF- β increased in AD as age advances. But in that respect, the important difference between nondemented persons and AD patients, is that in the AD

*Corresponding author. Tel.: 415 563 0818; Fax: 415 563 0818.

E-mail address: jeffreyfessel@gmail.com

brain the receptor for TGF- β , that is, TGFR2, is about 50% lower than normal, which minimizes the downstream neurotrophic benefits of the high levels of TGF- β . Thus, even higher levels than those observed in AD are required to overcome the bottleneck effect of low T β R2 levels. The above data suggest a hypothesis that low levels of brain TGFR2 plus an inadequately high level of TGF- β 1 and TGF- β 2, account for the strong correlation between AD and age. The heuristic value lies in the fact that drugs are available that will increase the levels of TGF- β . Following is the detailed evidence providing for the above statements.

1.3. Levels of TGF β -1 and TGF β -2 are stable until age approximately 85 then increase up to age 100+. Likewise, it is at age 86 when the annual incidence of Alzheimer's disease suddenly also increases

Young et al. [7] saw no difference in TGF- β levels between age 22 and 58; and Peterson et al. [8] showed that at ages 29.9 and 79, healthy individuals had identical levels of TGF- β . In healthy Japanese, there is either a slight fall in TGF- β levels between ages 40 and 79 [9] or no change between ages 17 and 70 [10]. However, at later ages, data reported by Forsey et al. [11] showed that the plasma level of TGF- β 1 suddenly jumped by 2.2-fold at age 86 as compared with age 32–59 and continued to rise at even higher ages so that it was 31% higher at ages 90–94 than at age 86. Likewise, Carrieri et al. [12] compared TGF- β levels in persons aged 20–60 with those of 73 centenarians. Male centenarians had 60% higher levels of TGF- β , and female centenarians had 27% higher levels, than had the younger males and females. In brief, in nondemented persons, there is a sudden rise in levels of TGF- β at the age of about 86, the same approximate age when there is also a sudden rise in the annual incidence of AD. Hebert et al. [13], estimated the future, annual incidence of AD in 1601 persons aged 65 and older who were initially free of AD. There was a 14-fold higher incidence at age 85+ than at age 65–69, and a 2.6-fold higher incidence at age 85+ than at age 80–84. Other data from Gao et al. [14] show that the incidence of all-cause dementia continues to rise so that at age 95+ it is now 37.5% more than at age 85–94. The inflection point is in the midninth decade of life.

1.4. TGF- β 1 and TGF- β 2 are neurotrophic

TGF- β 1 and TGF- β 2, interact with a receptor complex of ALK5 and TGR2; their binding to TGR2 causes its phosphorylation that in turn activates Smads, which are signal transducers that translocate to the nucleus and regulate gene expression. Most, but not all, reports show that in the brain, TGF- β 1 and TGF- β 2 cause neurotrophism, neural protection, synaptic transmission, and neural plasticity. Caraci et al. [15] found that administration of exogenous TGF- β 1 converted early-phase LTP into late-phase LTP; that

block of endogenous TGF- β 1 impaired LTP and object recognition memory, both rescued by administration of exogenous TGF- β 1; and that one of the effects of TGF- β 1 correlates with increased expression of pCREB, which has several beneficial effects on brain function [6]. Kandasamy et al. [16] showed that although TGF- β 1 promotes stem cell quiescence, it also promotes neuronal survival. Wachs et al. [17] studied neural stem and progenitor cells derived from the adult rat subventricular zone. TGF- β 1 markedly inhibited growth of those cells, whereas TGF- β 2 did not do so. Cell cycle analysis showed that TGF- β 1 induced a shift from the G2/M- and S-phases toward the G0/1 phase. However, TGF- β 1 did not affect expression of differentiating markers such as nestin, TGF-R2, or GFAP. Finally, a recent study showed that decrease in circulating TGF- β 1 prevented remyelination in toxin-induced demyelination and administration of exogenous TGF- β 1 promoted remyelination; and in an animal model of multiple sclerosis, TGF- β 1 restored neurologic function [18]. Related to this, Tarkowski et al. [19] found that MCI patients who converted to AD at follow-up had 30% lower TGF- β than had MCI patients who did not convert; and that those patients with MCI who did not progress to AD had closely similar (only 6.2% lower) levels of TGF- β than controls. Thus, the net overall effect of TGF- β 1 and TGF- β 2 is neurotrophic. An important effect of Smads is to effect transcription of genes that regulate micro-RNA formation which, as will be seen (below) determine, via TGFR2, whether local levels of TGF- β are adequate to support neurotrophism. For more details of TGF- β 's complex mechanism of action in the brain, the reader is referred to refs [15,20–22].

1.5. Even in the face of neuronal loss, TGF- β 1 and TGF- β 2 are paradoxically increased in the Alzheimer's disease brain

Neuronal loss is a critical early element in the genesis of AD, and although observations in patients with AD show varying blood levels of TGF- β [23–25], for CSF, which more closely reflects levels in the brain, all five reports showed levels of TGF- β 1 as being increased, from 1.1-fold to as much as sixfold [19,23,26–28]. Nevertheless and an apparent paradox, Buckwalter et al. [29] found that chronic overproduction of TGF- β 1 in mouse brains resulted in a profound decrease in neurogenesis. It is necessary to address this paradox, that is, that TGF- β 1 is neurotrophic, yet with high levels it impairs neurogenesis.

1.6. Explanation of the paradox. Levels of both Smads and TGFR2 in the brain of Alzheimer's disease are reduced, each of which serves to minimize the downstream, neurotrophic benefits of high levels of TGF- β 1 and TGF- β 2

In their review, von Bernhardt et al. [30] noted impaired Smad3 signaling but increased levels of activated

Smad2 in AD hippocampi and that phosphorylated Smad2/3 remains in the cytoplasm of neurons, instead of translocating into the nucleus. Tesseur et al. [31] examined the prefrontal cortex from 17 patients with AD of average age 80.5, and from 8 controls of average age 79.0. Compared with controls, the level of TGFR2 in AD brains was 50% less; and AD patients with MMSE scores 0–25 had significantly lower levels of TGFR2. Tesseur et al. also found in a mouse model of AD that reducing neuronal TGF- β signaling in mice resulted in age-dependent neurodegeneration and promoted A β accumulation and dendritic loss.

1.7. TGF- β 1, TGF- β 2, astrocytes, microglia, and age

Astrocytes produce both TGF- β 1 and TGF- β 2; Dhandapani et al. [32] demonstrated that both TGF- β 1 and TGF- β 2 are released by astrocytes and that both TGF- β 1 and TGF- β 2 are neuroprotective via phosphorylation and activation of c-Jun^{ser-63}. Astrocytes and microglia both have a unique signature that is dependent on TGF- β signaling [33] and have their anti-inflammatory activation repressed by TGF- β 1 [34]. Moreover, in the hippocampus, signaling by microglial TGF- β 1 via the Smad3 pathway is impaired in aging [35]. Mosher and Wyss-Coray pointed to the commonalities between the effects of aging and AD and suggested that “microglia may thus be primed such that additional stimuli cause them to become overreactive leading to neurodegeneration and AD” [36].

1.8. MicroRNAs and Alzheimer's disease

What determines that TGF- β is increased with age in both nondemented persons and AD? MicroRNAs (miRNAs) may be the explanation. MiRNA are noncoding RNAs containing only 22 nucleotides that can affect posttranscriptional expression of genes either positively or negatively; they are widely expressed in the brain and thus influence multiple brain functions. In Satoh's summary of 14 published studies of various miRNAs in the brains of 222 AD patients, downregulation of miRNA was 1.4-times more frequent than upregulation [37]. In a systematic review of the literature, Swarbrick et al. [38] found 27 articles that showed 250 miRNAs as being deregulated in the blood of AD patients compared with aged controls, and there was increasing deregulation with increasing Braak stage. A particular miRNA, 106b, was noted by Hebert et al. [13] as decreased in 19 patients with AD as compared with 13 controls, the significance of which is emphasized by the demonstration of Brett et al. [39] that the miRNA 106b-25 cluster promotes proliferation of neural stem cells (NSCs) and that knock-down of miR-25 decreased NSCs/progenitor cells' proliferation.

1.9. Which all leads to a hypothesis that one reason for the association of Alzheimer's disease with advanced age is that the decrease in TGFR2, possibly determined by deregulated miRNA, leads to reduced efficacy of TGF's neurotrophic effect

The hypothesis suggested here is that the basis of AD and its dependence on advanced age is the progressive decrease with advancing age in the numbers of TGFR2 receptors in the brain possibly caused by effects of an mRNA such as 106b. Its consequence is that the neurotrophic benefits of TGF- β 1 and TGF- β 2 are impaired and that in AD the compensatory increases of their levels in plasma and CSF are inadequate. The hypothesis may be supported by raising to adequate levels, for example, to double existing ones, TGF- β 1 and TGF- β 2, in patients with amnesic MCI and showing that this increase impedes the progression of MCI to AD.

1.10. Counterpoints to the proposed mechanism

Highlighted in this section are competing hypotheses relating age and AD together with counter-points. There are many factors with an undoubted pathogenetic effect yet few correlate with age. Notable suggestions to account for the age factor include roles for oxidative and free radical stress, mitochondrial dysfunction, insulin resistance, inflammation involving microglia and astrocytes, telomere shortening and other genetic aberrancies, and environmental inputs. There are counterweights for many of those suggestions.

Against oxidative stress is that healthy centenarians had lower oxidative stress compared with subjects aged 70–99, as shown by lower levels of malondialdehyde and higher levels of GSH [40]. Others have examined mitochondrial dysfunction and insulin resistance as accounting for the role of age in AD; but in fact those indicate participation of TGF- β 1, because Bohm et al. [41] demonstrated that TGF- β 1 induces insulin resistance but also downregulates mitochondrial genes. They studied the effects of TGF- β 1 on metabolic parameters of human skeletal muscle cells in culture and showed significantly decreased amounts of mRNA for PPARGC1A, PRKAA2, the mitochondrial transcription factor TFAM, and key regulators of oxidation, HADHA and CPT1B. Those decreases were prevented by cotreatment with the TGF- β 1 receptor 1 antagonist SB431542. It is notable that TGF- β 1 treatment of myotubes also had an inhibitory effect on insulin signaling since it reduced insulin-stimulated phosphorylation of Akt/protein kinase B. Hoffmann et al. [42] provided supporting data for effects on mitochondria by showing that TGF- β 1 reduced complex IV abundance in myotubes.

Next, the role of inflammation in the brain has been examined quite extensively in connection with age and

AD. Blasko et al. [26] showed that senescence of the innate immune system can be associated with a proinflammatory status of glial cells. Mosher and Wyss-Coray have provided data that support a major role for changes in microglial functions in both the healthily aging brain and the AD brain, and this overlap could account for the association between age and AD [36]. A counterpoint to that suggestion is that Hoozemans et al. [43] saw a waning of inflammation with age in the brains of both controls and AD. They examined the presence of both microglia and astrocytes in many areas of the brains using antibodies against CD68 and HLA-DP/DQ/DR to identify microglia and against GFAP to identify astrocytes. In AD, they saw (Fig. 1 [43]) >twofold fewer microglia in those aged >80 as in those younger than age 80, and threefold fewer astrocytes in those aged >80 as in those younger than age 80. Further, a role for TGF- β 1 in the formation and function of microglia was established in extensive studies made by Butovsky et al. [33].

Environmental inputs to the pathogenesis of AD are well known and supported by the prevalence of AD in Africans living in Africa as being significantly less than in African Americans [44]. As already indicated, most of the above factors may apply at any age, not just in advanced age.

Concerning the role of genetic inputs, Pedersen et al. [45] explained that different estimates of heritability may be seen by prevalence and incidence studies because there is a decreased likelihood of survival bias in incidence studies as compared with prevalence studies, whereas incidence studies only capture exposures relevant for new cases rather than effects of lifelong exposures. In a prevalence study of twin pairs aged 65 or older, Gatz et al. [46] identified 65 twin pairs, with a concordance rate for AD among the monozygotic pairs of 67%, whereas for dizygotic pairs the concordance rate was 22%; they estimated heritability at .74 for the liability to AD, with the remaining variance attributed to environmental influences. In an incidence study, Pedersen et al. [45] identified a cohort of 662 pairs of twins aged 52–98, who at baseline were without symptoms of dementia and had been followed for an average of 5 years, during which time 5.8% was diagnosed with AD at a mean age of 83.9 years. There were 26 monozygotic twins among which at least one twin developed AD that in 5 (19.2%) of them was concordant; and there were 44 dizygotic twins among which at least one twin developed AD that in 2 (4.5%) of them was concordant. Their results based on incident cases suggest a lower heritability and greater influence of environmental influences than reported in previous twin studies of prevalent cases, and their results provided no evidence that heritability is lower in those older than 80 years of age than in younger ages. Although heritability estimates for incident disease were far lower than those for prevalent disease, the importance of genetic factors for liability to AD is considerable even late in life. Whether calculations of genetic influences are based on incidence or prevalence, their importance is indisputable; and it is relevant that the hypothesis proposed

here incorporates genetic influences via the role of Smads in the transcription of mRNAs, and the effect of miRNA on gene expressions. Finally, it is the issue of telomere shortening in AD, shown by Forero et al. [47] in a meta-analysis of 13 studies involving 860 AD patients and 2022 controls. It is unclear, however, if telomere shortening is anything more than a biological indicator, that is, a surrogate, of the aging process.

Together, the factors mentioned in this section may be regarded as forming a complex system in which, as explained elsewhere [6], all of the factors interact in interdependent ways. It might be argued, based on complexity theory, that the reason why age is involved is because after a certain number of years, one or more interactions become more intense and exceed a critical threshold, causing the equilibrium to partially collapse, leading to MCI; and later, additional factor(s) or a heightened intensity of existing ones, results in complete system collapse and dementia. Nevertheless, that scenario is inadequate because it does not explain precisely why the time duration causing changes in cognition, whether MCI or AD, does not apply to far younger persons—of age, for example, 30–40 years—than is observed. An explanation suggested by Gatta et al. [48] is based on overlapping changes between AD model mice at 3 months of age and wild-type mice at 12 months of age, indicating the possibility that expression of aging-related genes occurs earlier in AD, which is certainly plausible and could depend on miRNAs. Supporting this, Podtelezchnikov et al. [49] examined three different regions in >600 brains from nondemented controls, patients with Huntington's disease, and patients with AD, representing >31,000 unique genes. Their analysis indicated that the same expressions of genes and the major biological processes initiated thereby, started in the PFC of normal brains and continued in AD brains; although principal component analysis showed significant correlation with normal aging ($\rho = .58$), that correlation did not exist in AD brains ($\rho = .10$). Podtelezchnikov et al. calculated what they term a BioAge score, which is based on the mean expression levels of the comprising genes at different ages. They found that the BioAge of the most advanced AD brains corresponds in nondemented subjects to an extrapolated age of 140 years.

In brief, the aggregate of genetic studies suggests strongly that gene expression is a possible reason why age is a major risk factor for AD. The pragmatic problem with this, however, is twofold. First, it recalls the statement attributed to Albert Einstein, “everything should be made as simple as possible, but not simpler”; the gene expression hypothesis is anything but simple because of the large number of genes that it invokes. Second, even though it cannot be made simpler, the multiplicity of gene expressions inherent in the explanation prevents it from the requisite of being validated.

A different and far simpler argument, consistent with Einstein's dictum, is basically the hypothesis proposed

here, that places TGF- β 1 as the single element determining outcome because it controls so many of the other participating factors. Two observations together explain both the deteriorated cognition leading to AD and old age as being the dominant risk factor. First that TGF- β 1 increases dramatically in normal aging, especially after age 86 in humans [11], and in rats [50]. Second, that a decreased number of TGF- β receptors with advancing age of the brain, reduces the effective neurotrophism of TGF- β despite its increased level.

1.11. Validation of the hypothesis

The hypothesis could be validated by increasing the levels of TGF- β and demonstrating that this prevents progression of aMCI to AD. Several drugs are available that increase the levels of TGF- β : those known to act in the brain and not only in peripheral blood include glatiramer, lithium, memantine, and venlafaxine. Lithium and memantine are interesting because they are among the drugs suggested elsewhere as potentially useful in decreasing the progression from aMCI to AD (Fessel J. TRCI 2019, In Press).

002Lithium approximately doubled the production of TGF- β 1 by cortical astrocytes [15]. Lee et al. [51] gave memantine in a dosage of only 5 mg daily to a group of patients in a methadone maintenance program to determine if the resulting, changed cytokine levels was beneficial; after 12 weeks, the level of TGF- β 1 was significantly increased. Glatiramer was shown by Aharoni et al. [52] to approximately double the amount of TGF- β produced by TH2 lymphocytes in the brain. Finally, Zepeda et al. [53] found that venlafaxine increased the production of TGF- β by approximately fivefold in the penumbra of a cerebral infarct and by >threefold in the unaffected hemisphere.

The outline of a clinical trial that could be used to validate the hypothesis was provided elsewhere (Fessel J. TRCI 2019 In Press). Because there is no basis for knowing by what degree the production of TGF- β needs to be raised a combination of three drugs should be used in a clinical trial: lithium plus memantine, together with either glatiramer or venlafaxine. That triple combination would be administered to patients with aMCI, and its effect assessed on their progression to AD.

2. Conclusion

Evidence supports the hypothesis that the reason for the association of older age with AD is a level of TGF- β that is rendered inadequate because of decreased brain levels of its receptor TGFR2. Validation could be obtained by a clinical trial assessing whether raising brain levels of TGF- β in patients with aMCI, by using lithium and memantine, together with either glatiramer or venlafaxine, impedes progression to AD.

RESEARCH IN CONTEXT

1. Systematic review: Published data show TGF- β is neurotrophic; in healthy individuals, its levels are stable until ~85 years of age then increase up to the age of 100+ years; coordinately, the annual incidence of Alzheimer's disease (AD) also suddenly increases after the age of 85 years; just as TGF- β levels in healthy individuals aged 85–100+ years, its levels are, paradoxically, also increased in the brain of patients with AD; but levels of TGF- β receptor 2 (TGF β R2) is only 50% of the normal level in the brain of patients with AD; compared with the aged controls, microRNAs in AD are deregulated, and there is increasing deregulation with increasing Braak stage.
2. Interpretation: The aforementioned data suggest a hypothesis that one reason for the association of AD with advanced age is that the decrease in TGF β R2, possibly determined by deregulated microRNAs, leads to reduced efficacy of TGF- β 's neurotrophic effect.
3. Future directions: The hypothesis may be validated by increasing the levels of TGF- β and demonstrating that this overcomes the bottleneck caused by diminished TGF β R2 and prevents the progression of amnesic mild cognitive impairment to AD. Glatiramer, lithium, memantine, and venlafaxine are available drugs that increase levels of TGF- β ; a triple combination of lithium and memantine plus either glatiramer or venlafaxine might be used in a clinical trial to assess whether this impedes the progression from mild cognitive impairment to AD.

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