The concept of inflammation as a major factor in Alzheimer disease (AD) has heretofore been based on postmortem findings of autodestructive changes associated with the lesions coupled with epidemiological evidence of a protective effect of anti-inflammatory agents. Now there is evidence that the risk of AD is substantially influenced by a total of 10 polymorphisms in the inflammatory agents interleukin 1α, interleukin 1β, interleukin 6, tumor necrosis factor α, α2-macroglobulin, and α1-antichymotrypsin. The polymorphisms are all common ones in the general population, so there is a strong likelihood that any given individual will inherit 1 or more of the high-risk alleles. The overall chances of an individual developing AD might be profoundly affected by a “susceptibility profile” reflecting the combined influence of inheriting multiple high-risk alleles. Since some of the polymorphisms in question have already been linked to peripheral inflammatory disorders, such as juvenile rheumatoid arthritis, myasthenia gravis, and periodontitis, associations between AD and several chronic degenerative diseases may eventually be demonstrated. Such information could lead to strategies for therapeutic intervention in the early stages of such disorders.

Interleukin (IL)–1α, IL-1β, IL-6, tumor necrosis factor α (TNF-α), α2-macroglobulin (A2M), and α1-antichymotrypsin (ACT) are all up-regulated in tissue from subjects with Alzheimer disease (AD) and are prominently associated with AD lesions. The inflammatory cytokines IL-1, IL-6, and TNF-α are products of both activated microglia and activated astrocytes that powerfully stimulate their activity. Localization of these cytokines to such activated cells has been demonstrated in AD by immunohistochemical analysis. α1-Antichymotrypsin is a product of activated astrocytes that is localized to beta-amyloid (Aβ) deposits in brains affected with AD. It has been suggested that ACT plays a role in plaque formation by enhancing conversion of nonfibrillar forms of Aβ to insoluble Aβ fibers. α2-Macroglobulin is a potent, broad-spectrum protease inhibitor thought to have evolved as a primitive host defense mechanism. α2-Macroglobulin and its principle receptor, low-density lipoprotein receptor, function as a clearance system for inflammatory proteins. They are detected immunohistochemically in association with neurofibrillary tangles and senile plaques in brains affected with AD.

The strongest evidence of polymorphisms in inflammatory agents increasing the risk of AD involves the IL1 complex. Chromosome 2q14-21 contains a cluster of IL1-related genes, including IL1A, IL1B, and IL1 receptor antagonist protein, all of which have significant polymorphisms. The IL1A–889 regulatory region exists in C (allele 1) and T (allele 2) forms. Four groups have now reported that carriers of the T form have an increased risk of AD. Grimaldi et al found a strong association between the T/T genotype and early-onset AD (odds ratio [OR], 4.86), with disease occurring 9 years earlier in T/T compared with C/C carriers. In their case-control study of 318 Italians, 17% of patients with AD and 9% of control subjects were of the T/T genotype.
Nicoll et al.\(^5\) studied a British and US case-control series of 399 individuals. They found that the IL1AT/T genotype occurred in 12.9% of AD patients compared with 6.6% of controls, confirming the general results of Grimaldi et al.\(^4\) Du et al.\(^6\), studying a US and German case-control series of 451 individuals, found that the T/T genotype occurred in 8.1% of AD cases and only 1.6% of controls. Statistical analysis following adjustments for sex and age group indicated an AD vs control OR of 7.2 for homozygous T/T carriers and 1.68 for heterozygous T/C carriers. Rebeck\(^7\) analyzed yet another case-control series of 434 individuals from Massachusetts. He found an OR of 3.1 for early-onset AD compared with the control group; 9% of his controls carried the T/T genotype compared with 23% of early-onset AD cases, although only 10% of AD cases overall were T/T. Although these case-control studies essentially confirm each other, they indicate a considerable variation in the frequency of T/T carriers in control populations. In fact, statistical tests suggest nonhomogeneity in the control populations. Obviously, studies of this kind are prone to type I and type II statistical errors. It will be important in the future to determine the influence of ethnicity on allele frequency, as well as to rule out, to whatever extent possible, the existence of latent disease in control populations. In these studies, allowance was made for ApoE4 (the gene for apolipoprotein E4) as a confounding factor, but numerous other polymorphisms may have influenced the outcome.

Two common polymorphisms in the IL1B gene have been reported to increase the risk of AD. These are located at the −511 position of the regulatory region, where T and C alleles exist, and in the +3953 position in exon 5, also where T and C alleles exist. Grimaldi et al.\(^4\), using the same population as for their IL1A genotyping, found that the T/T genotype for the −511 polymorphism was associated with a slightly increased risk for late-onset AD (OR, 1.95). Nicoll et al.\(^1\) reported on the IL1B +3953 polymorphism. Homozygosity for the +3953 T allele is reported to increase IL-1\(\beta\) production 4-fold compared with homozygosity for the C allele.\(^3\) They found the +3953 T/T genotype to occur in 7.3% of AD patients and 4.8% of controls. When they analyzed for simultaneous inheritance of the T/T alleles for IL1A −889 and IL1B +3953, the OR for developing AD rose to 10.8.

Interleukin 6 is a potent inflammatory cytokine that is hardly detectable in the central nervous system of healthy adults. However, it is rapidly induced in a variety of pathologic situations. Papassotiropoulos et al.\(^8\) found the C allele of the VNTR region to be protective against AD (OR, 0.60), delaying the initial disease onset. Licastro et al.\(^9\) in their case-control series of 448 AD cases and controls from an Italian population,\(^9\) found the D allele to have an opposite effect, ie, it increased the risk of late-onset AD (OR, 1.42). They confirmed the findings of Papassotiropoulos et al.\(^8\) of a reduced risk of the C allele as well as absence of the D allele (OR, 0.53). They also found that the C allele of the C/G −174 promoter region was associated with a risk for late-onset AD (OR, 1.56) and that there was linkage disequilibrium between the −174 promoter and the VNTR region. Plasma levels of IL-6 were higher in the AD patients than in controls, with the highest levels occurring in patients carrying the VNTR D allele. These results demonstrate that some alleles of a given polymorphism can reduce the risk of AD, while others enhance it. It is significant that the high-risk D allele of the VNTR polymorphism is associated with the highest IL-6 plasma levels, indicating that there is a systemic manifestation of the polymorphism.

Investigation of TNF\(\alpha\) polymorphisms was initiated because genome screening had suggested a putative association of AD with a region on chromosome 6p21.3, which was within 20 centimorgans of the TNFA gene. Furthermore, the TNF −308 promoter A allele had previously been shown to be associated with autoimmune and inflammatory diseases, and it was also known to have stronger transcriptional activity than the G allele. Similarly, the TNFA microsatellite 2 allele, located approximately 7 kilobases upstream of TNF, had previously been associated with higher TNF secretion and a susceptibility to rheumatoid arthritis. No associations had previously been found for polymorphisms of the −238 TNF promoter region. Collins et al.\(^10\) genotyped 145 high-risk families, consisting of 562 affected and unaffected siblings for association of these 3 polymorphisms with AD. They found that the TNFA microsatellite 2 allele alone was significantly associated with AD (\(P = .04\)) but that the 2-1-2 haplotype for −308, −238, and the microsatellite polymorphism was even more strongly associated with AD (\(P < .001\)). These data provide a correlation between unbiased genome-linkage studies, polymorphisms known to promote inflammatory disease, and enhanced production of an inflammatory cytokine.

\(\alpha_1\)-Antichymotrypsin is an acute-phase reactant that is produced by activated astrocytes and is elevated in brains affected with AD. Licastro et al.\(^11\) investigated the combined effects of ACT and IL1B polymorphisms on the risk of AD as well as on levels of expression of the protein in plasma. The genotyping was performed in 281 patients with probable AD and 201 controls without AD. For this Italian population, the ACT T/T and IL1B T/T genotypes were slightly and independently increased in AD patients. The concomitant presence of the ACT T/T and IL1B T/T genotypes increased the OR for AD to 5.6. A study of plasma levels in a subset of patients showed that the plasma levels of ACT and IL-1\(\beta\) were increased in AD patients with T/T genotypes. This study is a further illustration of a robust increase in OR when high-risk alleles of multiple inflammatory agents are carried simultaneously. It is also another example of how high-risk alleles can manifest themselves by higher systemic expression of the protein in question.

As with TNFA, investigations of the role of A2M were initiated as a result of screening studies of the genome. In this case, linkage was found in the region of chromosome 12p, where A2M and its low-density lipoprotein re-
ceptor are found. Blacker et al12 tested for associations of polymorphisms in A2M with AD in the National Institutes of Health Genetic Initiative AD sample. This sample is a large collection of affected sibling pairs and other small families with AD. It is now being used as a reference standard by many laboratories. Blacker et al12 found that a deletion in the A2M gene at the 5′ splice site of exon 18 conferred an increased risk for AD (OR, 3.56). The OR was comparable to that for the ApoE4 allele in the same population, although this A2M-2 allele did not affect the age of onset. These data did not confirm previously published linkage data to chromosome 12 and, in fact, have been challenged. Although further work is required on a larger population, the results strongly suggest involvement of the A2M gene in AD.

In summary, at least 10 polymorphisms involving 4 inflammatory cytokines and 2 acute-phase reactants have been shown to enhance the risk of developing AD. When 2 or more polymorphisms in linkage disequilibrium have been evaluated simultaneously, the risk has substantially increased beyond that of each one assessed separately. In most cases, the polymorphisms in question have also been linked to peripheral inflammatory disorders. In general, they have also been shown to correlate with increased production of the protein product. The overall implication is that individuals carrying 1 or more of these high-risk alleles are hypersensitive to abnormalities that provoke a chronic inflammatory response with consequent vulnerability to autodestructive processes.

If risk factors operate independently, the overall OR should be the product of individual ORs. In the case of AD, where the prevalence doubles every 5 years beyond age 65 years, each doubling of the overall OR should reduce the average age of onset by 5 years. Given that each of the 10 polymorphisms described above significantly affects the OR, their overall impact could be severe. More detailed genetic analyses in the future should make it possible to estimate a susceptibility profile for the development of AD with much greater accuracy. Perhaps other chronic inflammatory diseases will be included. Such information could prove valuable in devising strategies for therapeutic intervention, either before disease onset or in its early stages. This is particularly important for AD, because the inflammation is silent and the consequences are devastating.

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