Molecular mechanisms that alter the incidence and rate of neuromuscular disease progression are, in many cases, only partially understood. Several recent studies have asked whether apolipoprotein E (apoE for the protein, APOE for the gene) influences these aspects of specific neuromuscular disorders, as it does in central nervous system disorders such as Alzheimer disease. Although these studies are open to methodological criticism, several interesting trends have emerged. First, the APOE4 allele seems to be associated with an increased risk for developing certain neuromuscular diseases, including diabetic neuropathy and human immunodeficiency viral neuropathy. Second, this allele appears to be associated with faster progression of some neuromuscular diseases, including diabetic neuropathy and possibly motor neuron disease. Third, the APOE2 allele seems to confer protection against developing certain neuromuscular diseases, including the amyotrophic lateral sclerosis (ALS)/parkinsonism/dementia complex of Guam. Finally, this allele is associated with a better prognosis in neuromuscular diseases such as motor neuron disease. The effect of various APOE alleles on neuromuscular diseases therefore parallels their influence on central nervous system diseases.

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Apolipoprotein E (apoE for the protein, APOE for the gene) is a widely distributed, well-characterized cholesterol transport protein that circulates in the plasma after being synthesized by the liver, spleen, and kidneys. It is the major apolipoprotein in the central nervous system (CNS), where it is synthesized by glia, macrophages, and neurons. It is also found in the peripheral nervous system (PNS), where it is produced by nonmyelinating Schwann cells, ganglionic satellite cells, and macrophages. In humans, apoE exists in 3 common isoforms: E2, E3, and E4, which differ at amino acid positions 112 and 158. Isoform E3 has a cysteine at 112, and an arginine at 158; E2 has cysteines at both positions; and E4 has arginines at both positions. The absolute frequency of these different isoforms depends on the population being studied, but the relative frequency is always similar, with E3 being much more common than E2 or E4. Apolipoprotein E has long been known to participate in the distribution and internalization of cholesterol and other lipids. Consistent with this, mutations in the APOE gene are associated with familial type III hypercholesterolemia.

In recent years, data from animal and in vitro studies indicate that apoE plays an important role in neural function. Transection of rat sciatic nerve, for example, results in increased synthesis of apoE by Schwann cells with marked accumulation in the distal nerve stump over several weeks. A similar response occurs in rat sciatic nerve exposed to tellurium and lead, suggesting that this is nonspecific for injury type. In contrast, when rat optic nerve or spinal cord is severed, local apoE synthesis increases but apoE does not accumulate in the damaged neurons. Since sciatic nerves regenerate and optic and spinal nerves do not, these observations have been used to argue that apoE may play a role in nerve regeneration. Challenging this hypothesis, crush injury to sciatic nerves

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in genetically engineered apoE-deficient mice results in morphologically normal regeneration at the light microscope level. However, when the ultrastructure of sciatic nerves in apoE-deficient mice is examined with electron microscopy, fewer and abnormally shaped small unmyelinated axons are found compared with wild-type animals, and the apoE-deficient animals have reduced sensitivity to noxious thermal stimuli. These results suggest that apoE might play a role in promoting the general health and survival of neurons. In vitro studies support and extend these observations, indicating that the role of apoE in regeneration and trophism might be isoform specific; E3 results in more robust neurite outgrowth and better protection from toxins than E4.

Although animal studies suggest a role for apoE in PNS abnormality, the strongest associations between apoE and human nervous system disease exist in the CNS. A significantly higher frequency of the APOE4 allele is found in patients with Alzheimer disease (AD) compared with controls. Each APOE4 allele increases the risk of developing AD and lowers the age of onset. In contrast, each APOE2 allele decreases AD risk and increases the age of onset. Functional outcome after intracerebral hemorrhage is worse in patients with an APOE4 allele compared with those without one. Patients with head injuries with an APOE4 allele have lower Glasgow Outcome Scores 6 months after injury than matched cohorts without APOE4 alleles. Boxers with APOE4 are more likely to show neurological deficits than those without the allele in the same number of fights. Finally, the presence of an APOE4 allele increases the likelihood of neurocognitive decline after cardiopulmonary bypass. Taken together, these observations indicate that APOE4 alleles might confer decreased resistance or response to CNS injury and disease, while APOE2 alleles might confer increased resistance or response.

APOE AND NEUROMUSCULAR DISEASE

Diabetic Neuropathy

The strongest association between APOE and PNS disease occurs with diabetic neuropathy. Tsuzuki and colleagues examined 158 non–insulin-dependent patients with diabetes for evidence of retinopathy, nephropathy (proteinuria) and neuropathy. Those with neuropathy were classified according to a unique severity scale. All patients had apoE phenotyping performed and were classified E2 (phenotypes E2/2 and E2/3), E3 (phenotypes E3/3) or E4 (phenotypes E3/4, E4/4). These 3 groups were well matched according to age, duration of diabetes, body mass index, and hemoglobin A1C. There was no difference between the groups in frequency of retinopathy or nephropathy. However, the apoE4 group had a higher frequency of neuropathy (39%) than the E3 (28%) or E2 (23%) group. Furthermore, patients in the E4 group were significantly more likely to have severe neuropathy than patients in the E3 group. Finally, among patients with severe neuropathy, those in the E4 group developed neuropathy significantly sooner than those in the other apoE groups. The small sample size and the unique classification used for neuropathy, which largely relies on subjective reporting, limit the utility of this study. Still, the data are in keeping with the associations found in the CNS: apoE4 is associated with worse neurological outcomes in patients with similar exposure to disease or injury.

Human Immunodeficiency Virus–Caused Neuropathy

Similar, though less convincing, data relate apoE with the neuropathy caused by human immunodeficiency virus (HIV). Over a 5-year period, Corder and colleagues screened 44 HIV-positive patients for symptoms of infection, acquired immunodeficiency syndrome–defining illness, or peripheral neuropathy. All patients had apoE phenotyping performed on their serum and were subsequently classified as either E4 positive (having at least 1 copy of the E4 isoform) or E4 negative. The 2 groups were well matched according to sex, race, age, education, and CD4 count, and no difference in progression of acquired immunodeficiency syndrome stage was noted between groups over the course of the study. On initial examination, however, apoE4-positive patients had a higher incidence of peripheral neuropathy (20%) than apoE4-negative patients (3%). Furthermore, over serial exams, apoE4-positive patients were significantly more likely to develop peripheral neuropathy. However, the sample size in this study was very small: only 11 patients were in the apoE4 group. A definition of the neuropathy is not given. The investigators who diagnosed the neuropathy may not have been blinded to the apoE status of the patients, and no controls were placed on the distribution of drugs used to treat HIV, many of which cause neuropathy themselves.

Motor Neuron Disease and ALS

Despite 4 large studies, the association between APOE and motor neuron disease (MND) and/or ALS remains controversial. Mui and colleagues were the first to look for this relationship. They examined 170 patients with “ALS” (which was not defined). Of these, 72 had sporadic disease, 77 had a family history with unknown genetic predisposition, and 21 had a family history of a superoxide dismutase (SOD1) mutation. Patients with ALS were compared with 1209 historical age-matched controls and 60 ALS-free siblings or spouses of the familial group. No difference in APOE allele frequency was seen in any of the ALS groups compared with the controls. No difference was found in ALS onset age or disease duration between patients with an E4 allele and those without. This study, and the other ALS studies to date, also used a small sample size. Only the patients with familial ALS were used in the analysis of disease duration, and only 43 of 72 patients with sporadic disease were included in the assay for onset age (the loss of the other 29 patients is not explained). Most seriously of all, this study failed to define criteria for diagnosing ALS.

Al-Chalabi and colleagues asked similar questions, but obtained different results. In their study, APOE genotyping was performed on 123 patients with MND (diagnosed by 2 consulting neurologists) and 121 geographically similar disease-free controls. The frequency of APOE4 genotypes in the MND patient group was not
significantly different from that in their controls; however, there was a trend toward the MND population having a higher APOE4 genotype frequency (27.6%) than the controls (21.5%). Furthermore, when the patients with MND were subdivided into those with limb-onset disease and those with bulbar-onset disease, the latter group had a significantly higher frequency of APOE4 genotypes than the controls (42.4%; P = .02). When the probability of survival was plotted as a function of time by Kaplan-Meier analysis, patients with E4 alleles had a slightly greater rate of death than patients without. Although this difference did not reach statistical significance, it translated to a median survival of 35 months for patients with an E4 allele and 49 months for patients without; this would seem clinically important.

This study again suffers from small sample size, especially in analyses of subgroups such as patients with limb onset and bulbar onset (the latter group included only 33 patients). Furthermore, it fails to define the clinical or electrical criteria used in making the diagnosis of MND, and does not specify the etiology of this condition in its patient group (aside from saying they did not have dementia, spinal muscular atrophy, or Kennedy syndrome).

Moulard and colleagues confirmed and extended the findings of Al-Chalabi et al. They examined 130 patients with sporadic ALS, defined as probable or definite by accepted criteria. These were compared with 675 geographically similar historical controls. No significant difference in APOE genotype frequency was found between patients with ALS and controls; however, there was a trend toward patients with ALS having a lower frequency of E2-containing genotypes (8.5%) than the control population (15%).

No relationship between ALS onset age and allele type was found in this study. No difference in ALS duration was found between patients with and without E4 alleles. Interestingly, though, a statistically significant difference in disease duration occurred between patients with and without E2 alleles; those with E2 alleles survived longer. Further, a statistically significant relationship between ALS onset location and allele type emerged; patients with E2 alleles were more likely to have limb-onset disease, whereas patients with E4 were more likely to have bulbar-onset disease. Among the patients with limb onset, those with E2 alleles survived significantly longer than those without. Among the patients with bulbar onset, those with E4 alleles got their disease at a significantly earlier age than those without. Aside from the small sample size, which is exacerbated in the subgroup analyses, this is a well-designed study.

Smith and colleagues found yet a different spectrum of relationships between MND and APOE genotype. They performed APOE genotyping on 155 patients with sporadic MND, but did not describe their criteria for diagnosing MND. Comparing their results with the controls in the study by Mui et al, they noted no significant association between APOE2 or APOE4 allele frequency and MND. Further, they failed to confirm the previously described relationships between allele frequency and location of disease onset. However, using a validated functional scale, they did note a trend toward faster progression of MND in patients with APOE4 alleles than in those without. Although the trend did not reach statistical significance, the authors suggest that it was clinically relevant; a 20-point decline in their scale (identified as “major disease exacerbation”) took 14.6 months for APOE4-positive patients and 23.3 months for APOE4-negative patients. As with its predecessors, this study suffers from a small sample size. Also, it fails to define or elaborate on the causes of MND in its patients, or to mention whether those diagnosing the MND were blinded to the patients’ APOE status.

Guamanian ALS/Parkinsonism/Dementia Complex

To date, 2 groups have looked for a relationship between APOE allele types and a neurodegenerative disease that causes an ALS-like picture, as well as parkinsonism and dementia, in the Chamorro population of Guam. Waring et al genotyped 12 patients with the clinical features of this condition and 12 disease-free Chamorros. No difference in APOE4 frequency was detected between the 2 groups; however, the frequency of APOE2 was substantially lower in the Chamorros with this complex (8.3%) than in the controls (33.3%). Bue and colleagues replicated and extended these results by genotyping an additional 17 diseased Chamorros. Again, patients with the disease were found to have APOE4 genotype frequencies similar to Chamorro controls; on the other hand, APOE2 genotype frequencies were considerably lower in patients with the disease (11.8%) than in controls. Both these studies used small samples, and did not rigidly define criteria for disease. However, they did use a proper control group: one exposed to the same risks for the disease being studied as the patients with the disease. Because the ALS/parkinsonism/dementia complex is believed to arise from an environmental toxin, the controls were fellow Chamorros living in the same area. The importance of this will be elaborated in the “Comment” section.

Inclusion Body Myositis

Inclusion body myositis (IBM) shares several biochemical features with AD, including abnormal tau metabolism and apoE and β-amyloid peptide immunoreactivity within cells. This prompted Harrington and colleagues to compare APOE allele frequencies in 11 patients with biopsy-proven sporadic IBM with 58 nondemented age-matched controls. This prompted Harrington and colleagues to compare APOE allele frequencies in 11 patients with biopsy-proven sporadic IBM with 58 nondemented age-matched controls. No significant difference in APOE2 or APOE4 allele frequency was found between the groups. However, there was a small trend similar to that seen in the diseases described above; the E4 allele was slightly overrepresented and the E2 allele slightly underrepresented in IBM patients vs controls. This study had an extremely small sample size. Within the diseased patients, differences in onset age and disease severity were not examined as a function of APOE genotype.

Familial Amyloidotic Polyneuropathy

The amyloid in familial amyloidotic polyneuropathy exhibits apoE immunoreactivity. This led Saunders and colleagues to compare APOE allele frequencies in 24 patients with this rare condition (which they did not de-
fine clinically) with a variety of historical control groups, including ones that were geographically similar. No significant difference in APOE4 allele frequency was found between the groups. This study suffers from a very small sample size, and from failure to rigorously define the disease being studied.

COMMENT

As seen in the human CNS,12-18 there is tantalizing evidence that APOE can influence the progression of disease within the human PNS. A single study shows that patients with diabetes, neuropathy, and the apoE4 isoform develop neuropathy at a significantly earlier age and have significantly more advanced stages of neuropathy than their counterparts without this isoform.21 Among patients with MND, 2043 of 4 published studies demonstrate trends toward APOE4 alleles being associated with faster progression of disease. The only study examining APOE2 and MND progression shows that patients with MND and APOE2 alleles live significantly longer than those without this allele.27 Although each of these studies is open to methodological criticisms, their results are consistent with one another and with the data on disease in the CNS: APOE4 is associated with a worse prognosis and APOE2 with a better prognosis for a given neurological disease. Associations between APOE allele type and disease progression have not been explored in the ALS/parkinsonism/dementia complex of Guam, in IBM, in amyloidic neuropathy, or in any other PNS disease.

There are a variety of mechanisms by which APOE could influence the progression of these very different CNS and PNS diseases. One broad hypothesis is that certain APOE alleles confer an altered resistance to disease. As mentioned above, there is in vitro evidence that the different isoforms of apoE confer different susceptibilities to oxidative stress.11 Such differences may be mediated in part by the neuron’s ability to use growth factors; indeed, apoE is known to bind and potentiate the survival-promoting activity of ciliary neurotrophic factor in vitro.39 Also, the size and shape of axons from APOE-knockout mice are morphologically similar to axons from rats treated with nerve growth factor antisera.40 An alternate broad hypothesis is that certain apoE isoforms confer an enhanced regenerative response to disease. In a variety of cell lines, for example, apoE3 is associated with increased neurite outgrowth, while apoE4 is associated with decreased neurite outgrowth.9,10,41 The altered regeneration may again be caused by an allele-specific use of growth factors. Alternatively, the response may depend on isoform-specific alterations in neuronal adhesion,42 cytoskeletal stability,43 or the use of lipids for the expanding cell membrane.

A separate and unresolved question is whether APOE allele types actually influence the incidence of PNS disease. Individual studies in diabetic neuropathy23 and HIV neuropathy22 suggest that this is the case: namely, that APOE4 alleles confer an increased risk of developing these diseases. Two studies on Guamanian Chamorros suggest that APOE2 alleles confer a decreased risk of developing a neurodegenerative disease characterized by features of ALS, parkinsonism, and dementia.33,34 These studies mirror the effects of APOE alleles on the incidence of AD.12-15 However, no study on ALS, MND, IBM, or amyloidic polyneuropathy has demonstrated that APOE alleles confer increased or decreased risks of these diseases. This discrepancy is hard to understand, especially in light of the similarities in cellular pathology between the ALS/parkinsonism/dementia complex, AD, IBM, and amyloidic polyneuropathy. The most likely explanation for these ambiguities is the inadequacy of the control groups. The ideal control group for these is one that has all the possible risk factors for developing the disease but does not manifest the disease. In diabetes (where the endocrinopathy is the major risk for neuropathy) and HIV (where the infection is the risk), it is easy to obtain the proper controls. Unfortunately, in ALS, MND, and IBM, we do not know all of the environmental or genetic influences that contribute to the risk of disease. Thus, it is impossible to obtain the proper control group. On the other hand, in the ALS/parkinsonism/dementia complex of Guam, the primary risk for disease is thought to be an environmental toxin,35 and disease-free controls from the same area who are exposed to the same toxin can be obtained. One can then determine whether APOE alleles might help explain why individuals with similar environmental history have differing susceptibility to disease. In the case of the Guamanian Chamorros, the frequency of APOE2 alleles in patients with the neurodegenerative disease becomes significant only when one realizes that geographically similar at-risk controls without the disease have one of the highest frequencies of APOE2 alleles in the world.33

In summary, there is preliminary and tantalizing evidence that APOE alleles influence the progression and incidence of a variety of PNS diseases. The effect seems to be similar to that found in CNS diseases: the presence of APOE4 confers an increased risk of disease and a worse prognosis, while the presence of APOE2 confers a decreased risk of disease and a better prognosis. Further studies using larger sample sizes, rigid and objective definitions of the diseases being studied, and the proper at-risk disease-free control groups are needed to solidify this important relationship.

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