

Guest Editorials

Apolipoprotein E and Functional Illness in the Elderly

Following on from the hypothesis of a role for the ApoE $\epsilon 4$ and $\epsilon 2$ alleles as risk and protective factors, respectively, for late-onset Alzheimer's disease (AD) came inevitable questions regarding other psychiatric conditions of late onset including depressive illness and schizophrenia. Is ApoE $\epsilon 4$ a risk factor in these diseases and do carriers have an earlier age of onset? Does ApoE $\epsilon 2$ have a protective role, with carriers of this allele having a later age of onset?

Studies (Forsell et al., 1997; Holmes et al., 1998; Zubenko et al., 1996) comparing ApoE allele frequencies in depressed aged subjects across differing ages of onset with frequencies in age-matched controls have found little evidence that carriers of the ApoE $\epsilon 4$ allele have an increased risk of developing depressive illness or have an earlier age of onset, but have found some, albeit modest, evidence that carriers of the ApoE $\epsilon 2$ allele are offered some protection from the disease with a delayed onset. Studies of ApoE allele frequencies in subjects with late-onset (over the age of 45 years) depressive illness have been inconclusive; one early study (Krishnan et al., 1996) showed evidence for an increased frequency of the ApoE $\epsilon 4$ allele in the late-onset group compared with both the early-onset group and controls, but another study

(Heidrich et al., 1997) found no such evidence. However, none of these studies have reported on age-of-onset effects of ApoE alleles in the late-onset group alone.

In regard to schizophrenia, an initial early report suggesting a positive association between the presence of the ApoE $\epsilon 4$ allele and schizophrenia (Harrington et al., 1995) has been refuted by more recent studies showing no association (Arnold et al., 1997; Jönsson et al., 1996; Joobar et al., 1996; Kimura et al., 1997; Powchik et al., 1997; Town et al., 1997; Zhu et al., 1996). Some of these studies have also looked at age of onset, with two reports (Kimura et al., 1997; Zhu et al., 1996) showing no association between carriers of the ApoE $\epsilon 4$ allele and age of onset and one report (Arnold et al., 1997) showing ApoE $\epsilon 4$ carriers to have an earlier onset. In keeping with this finding, one study (Howard et al., 1995) of patients with late-onset (over the age of 60 years) schizophrenia showed a low frequency of the ApoE $\epsilon 4$ allele compared with published data in controls.

In AD, the situation regarding coexistent functional illness and ApoE is even more complicated. Although an early study found a positive association between carriers of the ApoE $\epsilon 4$ allele and depressive illness (Ramachandran et al., 1996), later studies showed either no association

(Holmes et al., 1996; Lopez et al., 1997) or a negative association between carriers of the ApoE $\epsilon 4$ allele and depressive illness (Ballard et al., 1997; Cantillon et al., 1997; Lyketos et al., 1997) and a positive association between carriers of the ApoE $\epsilon 2$ allele and depressive symptoms (Holmes, 1996). Likewise the association between carriers of the ApoE $\epsilon 4$ allele and psychosis has been found in some (Ballard et al., 1997; Holmes, 1997; Ramachandran et al., 1996) but not all studies (Lopez et al., 1997; Lyketos et al., 1997).

Trying to make sense of these findings is not helped by the different approaches to the important issue of age of onset. Some studies group all aged subjects together with no age-of-onset division and others divide depressive illness and schizophrenia, in an analogous fashion to AD, into early and late illness based upon an often arbitrary dividing point. Both approaches have their faults. Grouping all subjects together is dangerous if genetic heterogeneity exists, and an emphasis on a rigid dividing point presupposes knowledge of genetic subgroups based on age of onset, which we do not yet possess. It is worth remembering that the assumption of genetic homogeneity in early-onset AD led to considerable confusion in early studies of this disease and that the age-of-onset effects of ApoE $\epsilon 4$ are largely restricted to late-onset AD.

However, even taking these points into consideration, it is clear that ApoE does not have a major role to play in depressive illness or schizophrenia when they are considered as homogeneous groups. On the other hand, contradictory reports regarding age-of-onset effects of both the ApoE $\epsilon 2$ and ApoE $\epsilon 4$ alleles in depressive illness and schizophrenia and the lack of large studies of subjects with

late-onset illness make it premature to rule out age-of-onset effects of these alleles in specific subgroups.

Is it possible to reconcile the associations found between ApoE status and late-onset functional illness with those found between ApoE status and functional illness in AD? In depressive illness, clinical genetic studies may offer some clues. First, depressive illness occurring for the first time in AD subjects has been associated with a greater frequency of depressive illness in first-degree relatives but not with a familial liability for dementia (Pearlson et al., 1990; Strauss et al., 1996). Second, late-onset depressive illness does not interact with ApoE $\epsilon 4$ to increase the relative risk of developing AD but is a greater risk factor for AD than early-onset depressive illness, with increasing risk ratios the shorter the interval between the onset of depression and the onset of AD (Steffens et al., 1997). These findings can be explained if, instead of acting as a simple genetic risk factor for depressive illness, ApoE is considered to be acting as a quantitative trait variable as regards age of onset in a specific subgroup of subjects, namely late-onset depressive illness. Thus if ApoE $\epsilon 4$ hastens and ApoE $\epsilon 2$ delays the age of onset of late-onset depressive illness, then it would be anticipated, as shown in a number of studies (Ballard et al., 1997; Cantillon et al., 1997; Holmes, 1996; Lyketos et al., 1997), that AD patients with depression would have a relatively low frequency of the ApoE $\epsilon 4$ allele or, alternatively, have a greater frequency of the ApoE $\epsilon 2$ allele. Schizophrenia, unlike depressive illness, is less clearly a risk factor for late-onset AD and there is little evidence to show that increasing age of onset is associated with a greater risk of developing AD.

Thus the relationship between ApoE, late-onset schizophrenia, and psychosis in AD is less clear, but it seems unlikely that a similar mechanism to that proposed above is operating here.

Regardless of whether ApoE will give some insight into the relationship between functional illness and noncognitive symptoms in AD, it is clear that if ApoE does have an age-of-onset effect in depressive illness and schizophrenia, then some insight will be gained into the role that ApoE plays in cell biology. Thus, neither depressive illness nor schizophrenia is associated with the hallmarks of AD, namely, increased deposition of amyloid or tangle formation. This makes it unlikely that ApoE acts as a direct risk factor for AD, but suggests that ApoE has a more general role to play. Future research might thus be more profitably spent by evaluating more closely the normal role of ApoE in the central nervous system.

REFERENCES

- Arnold, S. E., Joo, E., Martinoli, M.-G., Roy, N., Trojanowski, J. Q., et al. (1997). Apolipoprotein E genotype in schizophrenia: Frequency, age of onset, and neuropathologic features. *NeuroReport*, *8*, 1523-1526.
- Ballard, C., Massey, H., Lamb, H., & Morris, C. (1997). Apolipoprotein E: Non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *63*, 273-274.
- Cantillon, M., Harwood, D., Barker, W., St. George-Hyslop, P., Tsuda, T., et al. (1997). No association between apolipoprotein E genotype and late-onset depression in Alzheimer's disease. *Biological Psychiatry*, *41*, 246-248.
- Forsell, Y., Corder, E. H., Basun, H., Lannfelt, L., Viitanen, M., et al. (1997). Depression and dementia in relation to apolipoprotein E polymorphism in a population sample age 75+. *Biological Psychiatry*, *42*, 898-903.
- Harrington, C. R., Roth, M., Xuereb, J. H., McKenna, P. J., & Wischik, C. M. (1995). Apolipoprotein E type $\epsilon 4$ allele frequency is increased in patients with schizophrenia. *Neuroscience Letters*, *202*, 101-104.
- Heidrich, A., Thome, J., Rosler, M., & Baumer, A. (1997). Apolipoprotein E- $\epsilon 4$ allele frequency in late-onset depression. *Biological Psychiatry*, *41*, 912-914.
- Holmes, C., Levy, R., McLoughlin, D.M., Powell, J., & Lovestone, S. (1996). Apolipoprotein E: Non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *61*, 580-583.
- Holmes, C., McLoughlin, D. M., Powell, J., & Lovestone, S. (1997). Apolipoprotein E: Non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *63*, 274.
- Holmes, C., Russ, C., Kirov, G., Aitchinson, K. J., Powell, J., et al. (1998). Apolipoprotein E: Depressive illness, depressive symptoms and Alzheimer's disease. *Biological Psychiatry*, *43*, 159-164.
- Howard, R., Dennehey, J., Lovestone, S., Birkett, J., Sham, P., et al. (1995). Apolipoprotein E genotype and late paraphrenia. *International Journal of Geriatric Psychiatry*, *10*, 147-150.
- Igata-Yi, R., Igata, T., Ishizuka, K., Kimura, T., Sakamoto, S., et al. (1997). Apolipoprotein E genotype and psychosis. *Biological Psychiatry*, *41*, 906-908.
- Jönsson, E., Lannfelt, L., Engvall, B., & Sedvall, G. (1996). Lack of association between schizophrenia and the apolipoprotein E $\epsilon 4$ allele. *European Archives of Psychiatry and Clinical Neuroscience*, *246*, 182-184.
- Joobar, R., Rouleau, G., Fon, E., Lal, S., Palmour, R., et al. (1996). Apolipoprotein E genotype in schizophrenia. *American Journal of*

- Medical Genetics (Neuropsychiatric Genetics)*, 67, 235.
- Kimura, T., Yokota, S., Igata-Yi, R., Shono, M., Takamatsu, J., et al. (1997). Apolipoprotein E $\epsilon 2$ allele and early onset schizophrenia. *Neuroscience Letters*, 231, 53-55.
- Krishnan, K. R. R., Tupler, L. A., Ritchie, J. C., McDonald, W. M., Knight, D. L., et al. (1996). Apolipoprotein E- $\epsilon 4$ frequency in geriatric depression. *Biological Psychiatry*, 40, 69-71.
- Lan, T.-H., Hong, C.-J., Chen, J.-Y., & Sim, C.-B. (1997). Apolipoprotein E- $\epsilon 4$ frequency in patients with schizophrenia. *Biological Psychiatry*, 42, 225-227.
- Lopez, O. L., Kamboh, M. I., Becker, J. T., Kaufer, D. I., & DeKosky, S. T. (1997). The apolipoprotein E $\epsilon 4$ allele is not associated with psychiatric symptoms or extrapyramidal signs in probable Alzheimer's disease. *Neurology*, 49, 794-797.
- Lyketsos, C. G., Baker, L., Warren, A., Steele, C., Brandt, J., et al. (1997). Depression, delusions and hallucinations in Alzheimer's disease: No relationship to apolipoprotein E genotype. *Journal of Neuropsychiatry and Clinical Neurosciences*, 9, 64-67.
- Pearlson, G. D., Ross, C. A., Lohr, W. D., Rovner, B. W., Chase, G. A., et al. (1990). Association between family history of affective disorder and the depressive syndrome of Alzheimer's disease. *American Journal of Psychiatry*, 147, 452-456.
- Powchik, P., Friedman, J., Haroutunian, V., Greenberg, D., Altsteil, L., et al. (1997). Apolipoprotein $\epsilon 4$ in schizophrenia: A study of one hundred sixteen cases with concomitant neuropathological examination. *Biological Psychiatry*, 42, 296-298.
- Ramachandran, G., Marder, K., Tang, M., Schofield, P. W., Chun, M. R., et al. (1996). A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease. *Neurology*, 47, 256-259.
- Raymond, F. L., Simpson, J. M., Sharland, G. K., & Mackie Ogilvie, C. M. (1997). Fetal echocardiography as a predictor of chromosomal abnormality. *The Lancet*, 350, 930.
- Steffens, D. C., Plassman, B. L., Helms, M. J., Welsh-Bohmer, K. A., Saunders, A. M., et al. (1997). A twin study of late-onset depression and apolipoprotein E $\epsilon 4$ as risk factors for Alzheimer's disease. *Biological Psychiatry*, 41, 851-856.
- Strauss, M. E., & Ogrock, P. K. (1996). Confirmation of an association between family history of affective disorder and the depressive syndrome in Alzheimer's disease. *American Journal of Psychiatry*, 153, 1340-1342.
- Town, T., Fallin, D., Crawford, F., Walsh, S., Solomon, R., et al. (1997). Lack of association between the apolipoprotein E $\epsilon 4$ allele (ApoE $\epsilon 4$) and chronic schizophrenia. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 74, 451-452.
- Zhu, S., Nöthen, M. M., Uhlhaas, S., Rietschel, M., Körner, J., et al. (1996). Apolipoprotein E genotype distribution in schizophrenia. *Psychiatric Genetics*, 6, 75-79.
- Zubenko, G. S., Henderson, R., Stiffler, J. S., Stabler, S., Rosen, J., et al. (1996). Association of the ApoE $\epsilon 4$ allele with clinical subtypes of late life depression. *Biological Psychiatry*, 40, 1008-1016.

Clive Holmes, BSc, MRCPsych
 The Maudsley
 Institute of Psychiatry
 London, England