Early-onset Alzheimer’s disease in Scotland: environmental and familial factors

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Background Alzheimer’s disease (AD) is a common, complex, age-related disorder in which both genetic and environmental factors are important.

Aims To integrate recent studies on genetic and environmental factors in AD into a multi-factorial disease model.

Method Disease models to explain gene–environment interaction in cardiovascular disease are related to observations on AD.

Results Informative, community-based studies on the genetic epidemiology of AD are rare. Putative risk factors from the Scottish studies include increased paternal age in AD men and coal mining as paternal occupation in both AD and vascular dementia. Migration effects suggest that environmental factors in high-incidence AD areas are important during adult life.

Conclusions The studies summarised do not provide sufficient data to support a single comprehensive disease model of gene–environment interaction in AD. Future studies will require very large (≥600) sample sizes, molecular genetic analysis, and environmental data that span neurodevelopment and the period between disease onset and appearance of clinical symptoms.

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Most studies on the possible role of environmental factors in Alzheimer’s disease (AD) have used case–control methodology when seeking to relate differences in risk of AD to different exposures to putative environmental insults. Likely candidates include head injury (Mortimer et al., 1985, 1991); low social class, especially manual occupations (Frattigioni et al., 1993); and work with industrial solvents or printing (Graves et al., 1991; Chen et al., 1999a,b).

With the exception of pre-dementia head injury (Mortimer et al., 1985) no single environmental factor has proved robust enough to be detected in several unrelated studies (Whalley, 1991). The proportion of cases in an early-onset AD sample that can be attributed to head injury is significant but not high, being estimated at around 4% of all cases (Mortimer et al., 1991).

Measure of social class in older people are difficult to make and interpret, especially in semi-skilled and manual workers, because of age-related social drift downwards, which is particularly evident in women. Occupational studies in AD are made more difficult because of the likely long lag period between the environmental exposures of interest and the late onset of dementia. In many countries, dementing illnesses do not present to clinical services and epidemiological studies must rely on specially recruited community-based, clinical or ‘at risk’ samples. Such recruitment is expensive and demanding of time, money and expertise. Not surprisingly, therefore, progress in understanding the possible role of the environment in AD remains slow.

More-rapid progress is being made in studies on the molecular basis and classification of AD. Although early-onset AD can occur as an autosomal dominant disorder, most instances appear to be sporadic with little evidence of genetic susceptibility. Nevertheless, Selkoe (1999) asserted that: ‘estimates of the proportion of Alzheimer’s cases that are genetically based have varied widely from as low as 10% to as high as 40 or 50% and some investigators believe that almost all cases will be shown eventually to have genetic determinants’.

The evidence for any of these estimates is scanty. Most molecular genetic studies (quite rightly) focus on individuals selected from families multiply affected by AD. These studies have identified three genes in which mutations can directly cause AD. First, mutations in the amyloid precursor protein gene (APP) were reported (Goate et al., 1991; Murrell et al., 1991; Mullan et al., 1992), but these account for fewer than 0.1% of all early-onset cases. Two more implicated genes were identified on chromosomes 14 and 1 (Rogaev et al., 1995; Sherrington et al., 1995), termed pre-senilin 1 and 2, respectively (PS1 and PS2). Christine van Broeckhovens and her colleagues (Cruts et al., 1998), surveying the frequency of mutant APP, PS1 and PS2 genes in a consecutive series of 101 early-onset AD cases, detected no APP mutations and only seven with PS1 or PS2 mutations. These provide the best estimates yet of the proportions of early-onset cases attributable to established mutations.

A fourth gene on chromosome 19 is also implicated in AD but not as a causal factor. This is the apolipoprotein E gene (APOE) locus at which a polymorphism (APOE ε2, ε3 or ε4) is linked to expression of AD. The identification of the ε4 allele as a risk factor for AD was established in genetic linkage and linkage disequilibrium studies (Percik-Vance et al., 1991; Saunders et al., 1993; Strittmatter et al., 1993). The susceptibility to AD attributed to APOE ε4 is estimated at 50–60% (Nabantoglu et al., 1994) and remains the most robust finding in general population studies of AD. Age at onset, for example, is linked in AD in an ε4 dose-dependent manner (Corder et al., 1993) so that the presence of two copies of the ε4 allele (ε4 homozygous) increases the risk of AD at an earlier age than the presence of a single copy (ε4 heterozygous). There is also some evidence of a protective effect of the ε2 allele (Corder et al., 1994). The strength of the evidence in support of a major role for APOE genotype is such that models of disease transmission within large samples of families have become both feasible and potentially informative.
Many commentators recognise that the risk of AD is determined partly by APOE genotype and partly by some other genetic and/or environmental factors (e.g. Rao et al, 1996). The effects of APOE genotype and family history of dementia on risk of AD were examined by Jarvik et al (1996) in a complex segregation analysis of AD in 204 families. Within the limitations of what may have been too small a sample to be informative, the authors rejected all simple models of AD transmission. They concluded that more complex models were required to account for their observations and did not discount the contribution of multiple genetic factors or environmentally linked disease mechanisms. Models of disease transmission were also developed by Lindsay Farrer’s group at Boston University School of Medicine to examine the contribution of APOE genotype and to account for the effects of gender. In what became the largest and most informative collaborative study of its kind in AD, Farrer and his colleagues (Farrer et al, 1995) assembled diagnostic and genealogical data on 549 AD patients and their first-degree relatives. The relationship between APOE status and gender was not straightforward. Among male relatives, the risk of AD in the ε3/4 group was similar to that for the ε3/3 group. Among female relatives, on the other hand, the risk for the ε3/4 group was almost twice that of the ε3/3 group. This difference suggests that gender may influence the risk of AD in ε4 carriers.

The same group subsequently demonstrated that in the presence of the ε4 allele, a dominant model best fitted the data (Rao et al, 1996). Single-gene inheritance also best fitted the pattern of AD incidence in families lacking ε4, but the authors could not exclude more complex modes of transmission in these families. Their research on the influence of gender indicated that susceptibility to AD differed between men and women irrespective of APOE status. They concluded that AD is completely penetrant in women, but only 62–65% of men with a predisposing genotype developed AD. In part, the difference could be accounted for by the premature death of men who were ε4 carriers, as ε4 conveys susceptibility to cardiovascular disease (CVD) as well as to AD. The problem was addressed in a separate survival analysis of AD relatives, which showed that women had a higher risk of AD after adjustment for the effects of CVD deaths in men. This collaborative study presents what is probably the best example of a complex segregation analysis of carefully diagnosed AD patients. Epidemiological studies on late-onset AD meeting precise requirements were entered into a meta-analysis by Gao et al (1998) to determine the contributions of age and gender to AD. As reported for early-onset AD (McGonigal et al, 1993), Gao et al (1998) found an increased risk of dementia in women. The work of the Boston group provides some clues to the likely biological explanations of this excess.

GEOGRAPHICAL DISTRIBUTION OF EARLY-ONSET AD IN SCOTLAND

Differences in the geographical distribution of early- or late-onset AD are reported but are not well understood. The first large-scale study identified differences between urban and rural populations, interpreted by Prince et al (1994) as “the protective effect of a rural environment”. Earlier, Gurland et al (1979) had found some evidence for a higher prevalence of age-related dementia in New York than in London. Geographical differences are perhaps most striking in studies of indigenous Black Africans from tropical Africa. Neuropathological studies found no AD in western African samples of demented and nondemented old people (Ountokun et al, 1991).

Geographical differences between countries – between urban and rural areas and within a single large city – pose many questions in AD about exposure to putative harmful environmental factors, the frequency of mutant genes in ‘at risk’ populations, the role of susceptibility genes (such as APOE) and the possibility that some environmental factors (e.g. the rural diet) are protective. Farrer’s group (Farrer et al, 1997) was the first to address the very real possibility that some exposures may censor ‘at risk’ populations, producing spurious gender effects. Their finding that the increased contribution of ε4 in women was not attributable to artefact is of considerable relevance to future studies in AD.

Scotland is well placed for the study of such complex interactions. Most of the population lives in a central belt running roughly west to east along a valley that divides the Southern Uplands from the Scottish Highlands. The western end of the belt contains over half the Scottish population in a conurbation of about 2.5 million people centred on the city of Glasgow. At the eastern end of the valley lies Edinburgh, the capital city. Traditional industries such as coal mining, steel production and shipbuilding have provided labour-intensive employment for most of the 20th century in the west. In the east, service industries and light manufacturing have predominated. Across this economic gradient in Scotland there is a well-established ‘health divide’. Age at death is lower, and death from vascular disease (notably cerebrovascular disease and myocardial infarction) more frequent in the west than in the east. These differences have been convincingly linked to socio-economic deprivation (McLoone & Boddy, 1994).

During the period 1955–1974, almost all early-onset AD cases presenting in Edinburgh came under the care of Dr Elizabeth Robertson. She had made AD her special interest, and having established post-mortem facilities in the principal mental hospital, she obtained neuropathological confirmation in 95% of her cases. Non-random geographical distribution of early-onset AD was demonstrated within Edinburgh with the highest incidence in an inner-city tenement area (Whalley & Holloway, 1985). Two apparently unrelated cases presented from the same apartment some 15 years apart. Previously, the pedigrees of all 69 cases had been examined in Register House, Edinburgh (Whalley et al, 1982). None of the cases shared common ancestors and no family members, as far as could be ascertained from death certificates, had died of causes or in circumstances suggestive of dementia. Analysis of the public water supply in 1986 to each address of presentation detected no differences between areas (unpublished observations).

Having detected a non-random distribution of pathologically confirmed early-onset AD in Edinburgh (Whalley & Holloway, 1985), we wished to examine this on a much larger scale. Specifically, we wished to test the proposed association between early-onset AD and aluminium content of the public water supply (Martyn et al, 1989), but this proved untestable largely because Scottish records revealed that the quality of the public water supply at any location has varied substantially over time. Variations arise partly because principal urban areas can switch between several alternative supplies as necessary, and partly because of continuous improvements in
water quality and analytical techniques during the lifetime of our subjects. Our approach was to examine geographical variation in early-onset AD using small-area geographical analysis (Whalley et al., 1995a). This relies on the division of the entire Scottish population into small areas (by postcode), each with about 5000 individuals. There was non-random geographical distribution of early-onset AD but not of the comparison conditions (vascular dementia, motor neuron disease, prostatic or ovarian cancers). These geographical differences could not be attributed to methodological artefact as other techniques of case-finding demonstrated the same differences between regions of Scotland. In the same study, there were geographical variations in early-onset vascular dementia and the frequency of cerebrovascular events, suggesting that some risk factors are shared between the two conditions (Starr et al., 1996).

Non-random geographical variation in the incidence of early-onset AD in Scotland was mostly located in small areas of the country’s densely populated central belt. These were concentrated in the large conurbations of Glasgow, the adjacent decaying industrial areas of North Lanarkshire and relatively impoverished areas of Edinburgh adjacent to the Lothian coalfields. Rural parts of Scotland were relatively spared (Thomas et al., 1997b). Earlier reports (Copeland et al., 1987; Prince et al., 1994) suggested that factors associated with urban life may increase the risk of early-onset AD, possibly through the same mechanisms that link urbanisation with increased incidence of cerebrovascular events (Starr et al., 1996).

In a second analysis of the epidemiology of early-onset AD in Scotland, we related geographical variation to exposures to possible risk factors. Once more, we found that Scotland had been subject to detailed epidemiological analysis so that a great deal was known about the ecology of socio-economic deprivation in this country. Carstairs & Morris (1991) classified all of Scotland’s small areas using a deprivation index based on an unweighted combination of four standardised variables (overcrowding, male unemployment, low social class and no car ownership). Socio-economic deprivation measured in this way was significantly related to the incidence of vascular dementia but not to that of early-onset AD. Contrary to expectations concerning hazardous exposures in some industries, specific occupations were not overrepresented among men with early-onset AD.

Surprisingly, increased paternal age was associated with early-onset AD in men but not in women. An earlier small study of AD in Scotland (Whalley et al., 1982) had detected increased parental age in AD. This observation was confirmed in other studies, but much later a larger study (Farrer et al., 1991) reported decreased paternal age in late-onset AD. This latter study contained sufficient statistical power to distinguish between maternal and paternal contributions to parental age effects in dementia. In the Scottish studies, the most plausible biological explanation of the putative association between increased paternal age and the incidence of early-onset AD would be that fresh gene mutation is more likely to occur with advanced paternal age, as reported in some studies that distinguish between ‘sporadic’ and ‘familial’ instances of autosomal dominant disorders such as Marfan’s syndrome (Emery, 1986). Increased paternal age and paternal cohabitation acted independently of one another and were not associated with specific geographical areas at the time of presentation.

Epidemiological studies of this type which can draw upon all relevant health data and public record statistics for a defined period of time (in this instance 1974–1988) prompt exploration of the temporal associations between exposures to various risk factors. Elegant statistical models are now available to examine the putative relationships between birth characteristics and later environmental established risk factors for hypertension and vascular disease (Elford et al., 1990). When differences are detected between geographical areas and there is sizeable migration between those areas, this can provide useful insights into the likely timing and mechanism of the environmental effect (Bentham, 1988).

The Scottish studies therefore allow related hypotheses to be tested by examination of the time from clinical presentation to death (survival time) in small areas of high incidence compared with those of low incidence (McGonigal et al., 1992; Thomas et al., 1997a). In addition, public record data provided information about place and circumstances at birth and presentation to hospital services. The length of survival after presentation with early-onset AD distinguished between areas of high and low incidence, in that patients presenting in high-incidence areas had significantly shorter survival times than those presenting in low-incidence areas. Those born in high-incidence areas who presented in low-incidence areas survived as long as those who were born and presented in low-incidence areas. Those born in low-incidence areas who presented in high-incidence areas had a shorter survival time.

The worse prognosis for early-onset AD could be explained by one or more of several factors. For example, it could be associated with a more severe variant of the disorder (Henderson et al., 1992). If our measure of migration (the difference between place of birth and place of presentation) is valid and approximates to environmental exposures in adult life, then it becomes plausible to argue that the decreased survival rate in those who are either born in or move to areas of high incidence is explained by exposure to the harmful effects of the environment in the high-incidence area. This inference is supported by the observation that those born in high-incidence areas but who moved to low-incidence areas where they presented had much better survival, confidently linked to mitigation of the disease process. A similar finding was reported by Horner & Chirikos (1987) in their study of survival in gastrointestinal cancers. Here, the complexity of the statistical model becomes evident; high-incidence areas for early-onset AD may also be characterised by increased incidence of other diseases that can cause premature death.

**GENETIC AND ENVIRONMENTAL RISK FACTORS: POSSIBLE LINKS**

Small areas of high incidence of early-onset AD may be explained by genetic relatedness such that mutated causal genes or genes that convey increased susceptibility to this disorder are more frequent in these localities. However, geographical variation related to locally increased gene frequency should be most obvious at time of birth and less obvious with the effects of migration over time. One of the limitations of our statistical analyses was that data on place of birth were insufficient to allow an informative analysis of geographical variation. However, other factors present at time of birth (paternal age and occupation) certainly contributed to the increased risk of early-onset AD. When we estimated the aetiological fraction attributable to other
established risk factors for AD we calculated that the proportion attributable to being female was 25%, to high paternal age 9.3% (male patients only) and to having a coal-miner father 10% (both genders). These factors together appear to act independently and contribute 45% to the total. A further 20%, we estimated, was attributable to environmental exposures in later life.

The effects of kinship

The genetic epidemiology of early-onset AD in Scotland may be partly explained if cases in high-incidence areas occurred more often among persons who were blood relations than might be expected by chance. Because this study was based on a historical cohort with few surviving members, informant histories were not available to us nor was it possible to obtain blood samples for genetic analysis. To address the question of genetic relatedness we developed a simple measure of the effects of kinship on the incidence of early-onset AD in Scotland. The hypothesis tested was that if a set of people with a certain characteristic, such as disease phenotype, are related to each other more often than would be expected by chance, then some familial contribution to that characteristic can be inferred. This familial contribution may then prove to have a genetic basis. We argued that the more often members of a set with a particular characteristic are related by blood, the greater the familial contribution to that characteristic.

Case kinship analyses of this type were undertaken for one area of high incidence in North Lanarkshire (Whalley et al, 1995a). We traced the ancestors of affected persons back to their great-grandparents’ generation from records held in Register House, Edinburgh. We used great-grandmothers as index-common ancestors, maternal relationship being more frequently specified on birth certificates than paternal relationship because of illegitimacy. When available, we used great-grandfathers’ names from marriage certificates and great-grandparents’ birth certificates to verify the correct identification of cases’ great-grandmothers. We estimated the ‘at risk’ ancestral population in this area of high incidence (North Lanarkshire) from census data between 1911 and 1921. We also recognised that the ‘at risk’ ancestral population requires a temporal as well as a spatial definition and so we used grandparental birth data of the early-onset AD cases to provide this.

The probability of two people being related to each other at the maternal, grandmaternal and great-grandmaternal levels is the product of the number of mothers, grandmothers, etc., of each person contained within the ‘at risk’ ancestral population (the method is detailed in Starr et al, 1997a,b). No shared great-grandmothers were found among early-onset AD cases presenting in the high-incidence area of North Lanarkshire.

Our estimates of the founder population of great-grandmothers in North Lanarkshire as a whole provided an ‘at risk’ estimate that allowed kinship by shared great-grandmothers to be calculated. The minimum kinship estimate was 1.84 and the maximum was 3.18. If there were no familial contribution to raised incidence in Lanarkshire, the kinship estimate range would have included 1.0. We concluded that in North Lanarkshire familial factors were probably involved but because of the small sample size (69) we could provide no direct evidence of this. However, part of the clustering of early-onset AD cases in Lanarkshire is probably caused by some familial contribution. This may act independently of the familial contribution to cerebrovascular disease (Starr et al, 1997a).

Paternal age and occupation

The observations that the fathers of men with early-onset AD were generally older, and more likely to be coal miners (19.8%), than the fathers of control subjects (9.8%) were unique, and require separate consideration. It is difficult to relate increased paternal age and specific occupations to a biological disease mechanism without first considering the possibility of paternal occupational exposure to a mutagenic hazard (e.g. as may occur in workers who process nuclear fuel) which might alter germ cells, reduce male fertility and increase the risk of specific disorders in offspring (as in the proposed increase in leukaemia among the children of nuclear fuel processing workers).

In a pioneering study of early-onset AD cases in Minnesota, Heston & Mastroi (1977) found increased familial incidence of Down’s syndrome and lymphomas. The familial link with Down’s syndrome has proved robust (van Duijn et al, 1991) and remains unexplained. Heston & Mastroi (1977) linked this observation to the possibility that a major gene effect in AD perturbed microfilament function, an essential component of cytoplasmic movements of all types (Smith, 1996). Impaired microfilament contractions would result in chromosomal non-disjunction (as in Down’s syndrome) – an idea that was developed further by Potter (1991). Motility of spermatozoa also relies on contractions of microfilaments and microtubules. Reduced spermatozoal motility causes decreased male fertility and this is sometimes associated with increased paternal age. Microtubules are composed of tubulin and are quite distinct from the microfilamental proteins, which are composed mainly of actin. Microtubules, like microfilaments, are also well known to be involved in cell movement. Tubulin is polymerised and stabilised with the help of microtubular assembly proteins. Tau is a microtubular assembly protein coded for by a single gene on chromosome 17. Several familial demencias are already linked to mutations of the tau gene (Spillantini & Goedert, 1998) but these do not include early-onset AD. Given the central role played by tau protein and its assembly in its hyperphosphorylated and abnormally phosphorylated form into paired helical filaments in AD, genetic contributions to AD that influence tau processing could prove important. Fresh gene mutations linked to increased paternal age and occupation may contribute to apparent sporadic AD cases.

Coal-mining families in Scotland in the early part of the 20th century were severely disadvantaged. Several adult-onset diseases are linked to deprivation in childhood and infancy, but so far no convincing case has been made to link such deprivation with dementia. Our studies linked paternal coal mining to early-onset AD and to early-onset vascular dementia, which suggests that this is a non-specific effect. Substantial data already link adult poverty to premature death and there are some data to support the hypothesis that childhood privations, perhaps beginning in utero, predisposed to early death from vascular disease (Williams et al, 1979; Barker et al, 1990; Hales et al, 1991; Barker & Martyn, 1992). Furthermore, other data also show that these associations vary over time and may even be increasing in some parts of the developed world (Forstahl, 1978; Doornbos & Kromhout, 1990; Eames et al, 1993; Kunst & Mackenbach, 1994).

The cerebral reserve hypothesis is proposed to explain individual differences in susceptibility to dementia (Satz, 1993; Schofield et al, 1995; Stern et al, 1995;
Mori et al., 1997). In normal neurodevelopment a 'reserve capacity' is acquired to withstand brain insults. When progressive brain disease supervenes, it must first overcome the 'cerebral reserve capacity' before symptoms of dementia appear. The privations experienced by the children of coal miners could be linked to a failure to acquire sufficient cerebral reserve capacity to withstand the onset of age-related neurodegeneration. Consequently, the symptoms of dementia (either AD or vascular dementia) tend to develop prematurely. The socioeconomic disadvantages of an early life spent in an impoverished household may be linked to the frequent observation that low educational attainments increase the risk of late-onset AD. Low educational attainment was also linked to restricted neurodevelopment (Porter & Pavitt, 1987), although the evidence is not strong (Deary & Caryl, 1997). Katzman (1993) and Mortimer et al. (1991) reviewed studies to date and concluded that one of several plausible biological explanations could be involved, but that the data at that time were hardly more than suggestive. Subsequent examinations (Evans et al., 1993; Stern et al., 1994; Cobb et al., 1995; Mortel et al., 1995; Plassman et al., 1995; Schmand et al., 1997a,b) of the proposed association do not as yet allow a firm conclusion to be drawn.

Snowdon et al. (1996) provided what became the best-known study on this question – largely, it seems, because their subjects (elderly nuns) were such an unusual sample. As in earlier studies, Snowdon and his colleagues were constrained by the lack of good-quality, well-validated measures of childhood mental ability and were obliged to use proxy data. (They ingeniously devised a mental ability measure from a sample of semi-autobiographical prose composed and archived on taking holy orders.) Final resolution of the proposed association between educational attainments and risk of dementia awaits the review of several well-studied ageing birth cohorts on completing most of the risk period for dementia and for whom systematic ability and educational data are available.

**CONCLUSION**

Brain diseases, age-related brain degeneration and neurodevelopment are discrete independent processes that are locked together in complex ways. There are varied influences on the processes of neural differentiation, maintenance and repair in the face of age-related disease and/or degeneration. A comprehensive multi-factorial model of early-onset AD must distinguish between genetic factors related to ancestral genes, fresh gene mutation, gender and age-related genes, the harmful effects on neurodevelopment of privations such as malnutrition in early life, and exposure to a harmful environment in mid-life. If the dietary environment includes nutrients with known advantages for nervous development (e.g. essential fatty acids in the early diet, or antioxidants in fresh fruit and vegetables in late diet), then the onset of a debilitating illness may be postponed. If it is also supposed that age at onset of AD is at least partly determined by exposure to a harmful environment in early life, this could implicate a reduction in the 'cerebral reserve capacity' available to adapt to insult, accelerating the onset of symptoms of dementia.

This brief review has focused on some of the most pressing problems in understanding the occurrence of AD. Genetic factors are of established importance and are intensively studied. The interaction between APOE status and gender provides a useful insight into the complexity of the issues and informs future researchers of the scale of effort required to disentangle the genetic and environmental factors involved. Despite their considerable effort in recruiting over 600 families, Lindsay Farrer's group expressed doubts that their sample size might still be too small to disentangle the complex factors involved (Farrer et al., 1995). Geographical distribution of a Scottish national sample of AD with post hoc kinship analysis of disease clusters provided a complementary approach to classic segregation analysis in large samples. Although each technique has its disadvantages, ecological data used alone will always be much less exact than those based on more direct study. However, some combination of the two approaches, with the added precision afforded by molecular genetic analysis, may provide the most informative solution. Such studies are now under way in at least three major centres worldwide. Their findings will help answer some of the many unanswered questions about the causes of AD. It is no longer speculative to propose that future clinical practice in dementia will be influenced by the results of epidemiological enquiry. Much as has occurred in the prevention of cardiovascular disease, individuals entering the risk period for dementia will be offered an assessment of their risk of developing the condition. The techniques of epidemiology will be in considerable demand to evaluate and refine the interventions thought likely to delay or even prevent the onset of dementia (Whalley & Struth, 1998, 1999; Selkoe, 1999).

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