Parkinson's, Alzheimer's, and motor neurone disease

See p 728

Clinical and pathological overlap may suggest common genetic and environmental factors

The label "neurodegenerative" is often used as an umbrella term for the distinct pathological conditions of Parkinson's, Alzheimer's, and motor neurone disease. However, there has been speculation that all three conditions represent different phenotypic expressions of a common aetiology.[1] Calne and colleagues have argued that these diseases are examples of selective, premature decay of functionally related populations of neurones due to interactions between the environment and the aging process.[2] Their two component hypothesis postulates that environmental insults, such as infection or neurotoxins, partially deplete selected neuronal populations, and that age related degeneration results in further neuronal loss beyond a threshold necessary for clinical disease. This model argues that age related cell death is a common contributory factor for all three diseases, although there may be specific environmental factors for each condition.

Epidemiological data show some superficial similarities. The incidence of all three conditions increases with age and seems to be increasing over time, although the latter might reflect both better ascertainment and the decline of other competing causes of death.[3] For both Parkinson's and Alzheimer's disease, non-smokers seem at greater risk of disease than smokers. Since smoking is related to an increased risk of a wide spectrum of diseases,[4] this shared inverse association is striking. One controversial hypothesis for this observation is that smoking interacts with non-specific "aging genes," removing from the population a larger proportion of smokers, who were susceptible to these diseases.[5] This "selective mortality" explanation is not readily supported by empirical evidence.[6]

At a clinical level, patients with Parkinson's disease are more likely to have dementia,[7] and similarly there is a greater than expected increase in extrapyramidal (parkinsonian) signs in patients with Alzheimer's disease, although frequencies vary between 28% and 92%.[8] Two recent publications support the clinical and pathological overlap of these two conditions.[9,10] Follow up of patients on a Parkinson's disease register showed an increase of more than threefold in relative risk of dementia compared to controls.[9] Among patients aged 50-54 years, the prevalence of dementia was 13 times greater than expected. Similarly, pathological data on 78 cases of Alzheimer's disease proved by necropsy showed that around 21% of cases had neuropathological features of Parkinson's disease.[10] These cases were more likely to have had premorbid extrapyramidal features but had fewer neurofibrillary tangles in the neocortical areas. The coexistence of all three conditions is rare except for the unusual syndrome of amyotrophic lateral sclerosis-parkinsonism-dementia complex seen on the islands of Guam and Rota.[11]

At a familial level, there is evidence that parents and siblings of patients with Alzheimer's disease have a threefold risk of Parkinson's disease.[12] This may reflect either shared environmental influences or genetic factors. Recently much excitement has been generated by the discovery that the apolipoprotein E ε4 allele is associated with an increased risk of Alzheimer's disease, cortical Lewy body dementia, and bulbar onset motor neurone disease.[13,14] There seems to be no such association for Parkinson's disease, in the absence of dementia.[15] In contrast, defective alleles of one of the cytochrome P450 genes, CYP2D6, are associated with Parkinson's disease, but not with either Alzheimer's or Lewy body disease.[16]

This suggests that if there are common genetic defects that are pathogenic in all three conditions they must involve genes other than those studied to date. It remains possible that the aberrant activation or function of one or more such genes could lead to the different pathologies, perhaps by differential interaction with various environmental factors. At a clinical level, it is important to understand the association between Parkinson's disease and dementia, as patients with both conditions will place far greater demands on their carers and the health care system. Given our current state of knowledge the overlap between these diseases raises further questions regarding pathogenesis rather than providing any immediate therapeutic solutions. Clinicians and researchers may learn much from discussing and further exploring the similarities and differences in the epidemiology, pathology, and genetics of these intriguing diseases.

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An editorial on alcohol and heart disease, linked to papers in this issue by Rimm *et al* and Hein *et al*, will accompany a third paper on the subject in the *BMJ* in May.