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# News from epidemiological studies on Alzheimer's and Parkinson's disease: a personal perspective

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Thousands of papers on neurodegenerative disorders and dementia are published every year in the most important scientific journals: thus, it is a hard task to synthesize the most novel findings. A reasonable solution is to report a personal point of view, considering research that challenges, reinforces, or contradicts commonly accepted scientific paradigms. Better understanding, and new avenues of research and knowledge, can be derived from a reasonable balance of these apparently contrasting conceptual premises.

In 2012 one of the most cited articles on Alzheimer's disease (AD) was the work of Bateman and colleagues [1] from the dominantly inherited Alzheimer network (DIAN), reporting on biomarkers of AD in a cohort of offspring of persons suffering from a dominant genetic form of AD caused by mutation in the gene of Presenilin-1 (PSEN1), Presenilin-2 (PSEN2), and amyloid precursor protein (APP). The study design included a comparison of different laboratory, instrumental, and clinical biomarkers of AD in carriers and non-carriers of the AD mutation against the estimated time to or from clinical diagnosis of dementia. This estimate was derived from the difference of the actual age of the participant and the age of onset of dementia of his/her parent. The findings identified a time sequence of modifications of cerebrospinal fluid (CSF), beta amyloid (Aβ), and tau protein concentrations, Aβ accumulation in the brain, reduced brain glucose metabolism, hippocampal atrophy, signs of cognitive impairment, and finally, clinically evident dementia. In mutation carriers, Aβ42 concentration in CSF declined 25 years before the expected symptom onset compared to non-carriers. Aβ deposition in brain, measured by PIB-PET, increased the levels of tau in CSF, and brain atrophy was detected with MRI approximately 15 years before the expected symptom onset. Cerebral hypo metabolism measured with FDG-PET and impaired episodic memory were measurable approximately 10 years before expected symptom onset and were followed by global cognitive impairment starting from 5 years before the expected symptom onset. Although these results were obtained with a cross-sectional study design and based on many assumptions, they nonetheless represent an appealing synthesis of what is generally accepted to be the pathogenic mechanisms of AD and the time sequence of alterations that the disease induces. The amyloid cascade leading to Aβ accumulation in the brain is toxic to vulnerable neurons; this toxicity is marked by the increase in concentration of the cytoskeleton tau protein into CSF. The neuronal degeneration and functional impairment is documented by brain atrophy on MRI and FDG-PET examinations. All these manifestations precede the time at which the signs of the disease are sufficiently severe to meet the clinical criteria for a diagnosis of dementia and might precede any signs of impairment in cognitive performance. This study provides strong support to the common and reasonable idea that AD pathogenic processes precede the clinical manifestations of dementia by a long time period and that interventions might, and possibly should, be targeted to the early phases of the disease.

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A hot topic in current neurodegenerative research includes the novel and somewhat unanticipated findings that have been reported in recent studies investigating the relationship between cancer and neurodegeneration. The first study by Driver and colleagues [2] reports results from the Framingham heart study on an inverse relationship of occurrence between cancer and AD. This is a prospective cohort study where persons with and without a characteristic of interest are followed a long time for the occurrence of specific outcomes. Much of the current knowledge on vascular risk factor descends from the results of the Framingham heart study, but in more recent times the Framingham researchers have paid attention also to the determinants of dementia and more generally to cognitive decline in aging. In Driver et al.'s study, 176 participants had a history of cancer at baseline, and 247 were diagnosed with cancer during a follow-up of 10 years. Persons with cancer had a 30 % reduction of the risk of occurrence of probable AD, which was even lower (70 %) in persons with non-smoking related cancers. These findings on AD mirror what has already been observed for Parkinson's disease (PD), where a relatively large number of studies report a reduced risk of cancer [3] suggesting that neurodegenerative processes in general may characteristically have an inverse relationship of occurrence with cancer. The perception of clinicians is that AD patients are more healthy than persons of the same age and sex, and at least two formal epidemiological studies by Roe and colleagues [4, 5] on two independent sets of data have reported a reduced risk of cancer in persons with AD, and vice versa. It has to be considered that some confounding, non-causal, factors can determine the observation of lower occurrences of cancer in persons with dementia and vice versa [6]. Firstly the fact that, in patients with AD or cancer, any new occurring sign or disturbance might be interpreted as a consequence of the already-diagnosed, primary disease. Anyway these data can be tentatively, and more interestingly, interpreted in the light of senescence, which is the negative characteristic that inevitably accompanies aging. Neurodegeneration and cancer are processes related to aging, but are opposite phenomena that characterize two different ways of becoming senescent [7]. However, we are only beginning to identify and understand this complex story. A well-designed epidemiological study by Kareus and colleagues [8] recently reported results from the Utah cancer registry showing that even though the risk of cancers in general is reduced in relatives of PD patients, the risk is increased for prostate cancer and melanoma. This study suggests that common genetic determinants are involved both in cancer and PD (possibly in cancer and neurodegeneration), but that these common determinants might exert a differential action according to cancer type. It is evidence that before drawing conclusions on the relationship between cancer, AD, and PD, more studies are needed to identify the specific role of cancer in neurodegenerative disorders.

**Conflicts of interest** None.

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