Association Between Alzheimer Disease and Amyotrophic Lateral Sclerosis?

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ABSTRACT: We report two cases of Alzheimer disease (AD) — one of them familial — in which the patient also had amyotrophic lateral sclerosis (ALS), and one patient with familial AD who had a son with ALS. Three further cases of probable ALS were found in pedigrees of AD reported from the literature. It is proposed that this association is not coincidental, but may suggest an etiological factor in common.

RÉSUMÉ: Association entre la maladie d'Alzheimer et la sclérose latérale amyotrophique Nous rapportons deux cas de maladie d'Alzheimer (MA) - dont un cas familial - où le patient était également atteint de sclérose latérale amyotrophique (SLA), et un patient atteint de MA familiale qui avait un fils atteint de SLA. Trois autres cas de SLA probable ont été trouvés dans des pedigrees de MA rapportés dans la littérature. Nous proposons que cette association n'est pas une coïncidence, mais peut suggérer un facteur étiologique commun.

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Selective neuronal degeneration occurs in Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD), affecting in each case specific pathways within the nervous system. Some individuals have more than one of these conditions as with neuropathologically confirmed PD in AD patients,[1] and in the Guamanian ALS-PD complex with or without Alzheimer changes.[2]

Whether these three disease processes have an etiological factor in common has been the subject of speculation. Their cause has been attributed to lack of a disorder-specific neurotrophic hormone stored in postsynaptic target cells such as cortical cells in AD, muscle cells in ALS and striatal cells in PD, which acts in a retrograde fashion on the presynaptic terminal.[3] A single pathogenic mechanism, namely interference with axonal transport, has been postulated for neuronal degeneration.[4] A unifying model linking the three diseases to environmental damage, of toxic or infectious origin, has been proposed[5] with the neuronal damage remaining subclinical until a threshold in the natural aging process is reached, after which the disease becomes manifest. Recent studies have shown that markers on chromosome 21 that are linked to Alzheimer disease have positive lod scores in familial ALS, but linkage has not been established.[6]

In support of the hypothesis that AD and ALS may have a causal factor in common, we present from our own observations, and from the literature, two cases of ALS and AD occurring in the same patient, and three confirmed and two probable cases of ALS in families segregating for AD.

Patients and Families

Case Reports

Family 1

A woman with both ALS and AD died at age 70, three years after the diagnosis of ALS at the Montreal Neurological Institute. She had presented with a progressive weakness of her left arm, and subsequently developed problems with her right arm, bulbar musculature and legs. She did not appear to be demented; one year prior to death, only her physical disability had prevented her from doing housework, and she had continued to communicate with a typing machine. ALS was confirmed at autopsy with anterior horn cell loss in the cervical and lumbar enlargements (Dr. Y. Robitaille). AD was determined only at autopsy with slight atrophy in the temporal area bilaterally, and neurofibrillary tangles and plaques predominantly in the temporal lobe and the hippocampus. No other family member had either disease. Her mother died at age 96 of cardio-renal failure, and her father died at age 67 of myocarditis. He was from Newfoundland, but could not be linked with any of the families in the Newfoundland Alzheimer study.

Family 2

ALS was diagnosed at the Montreal Neurological Institute by clinical examination and electromyograhy in a 65-year-old woman who presented with difficulty in walking and frequent falls. Within months the patient displayed severe behavioural problems with marked aggressiveness accompanied by a decline in recent memory, new learning deficits and constructional apraxia, but with fairly well-preserved orientation, language function and ability to abstract. This was felt to be an atypical picture of AD. There was further deterioration of the ALS process with dysphagia and she died of bronchopneumonia six months after the initial diagnosis of ALS. Although the brain showed no general atrophy, neuropathology confirmed ALS with extensive drop-off of motor neu-

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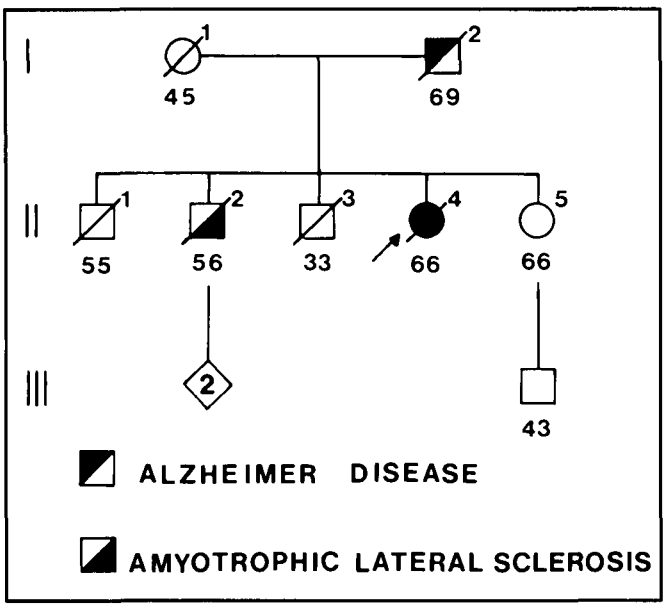

Figure 1 — Pedigree of a Montreal family with Alzheimer disease and amyotrophic lateral sclerosis (Family 2).

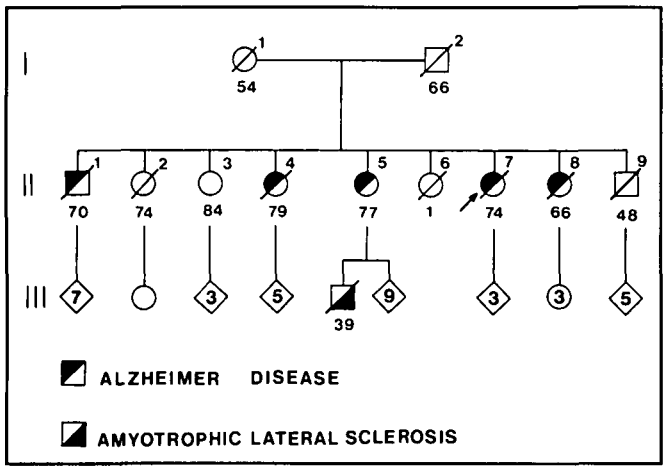

Figure 2 — Pedigree of a Newfoundland family with Alzheimer disease and amyotrophic lateral sclerosis (Family 3).

rons around the spinal cord and a severe type of AD, with an abundance of neurofibrillary tangles, predominantly in the hippocampus, and senile plaques particularly in the frontotemperoparietal region (Dr. Y. Robitaille). There was a family history of both conditions; neither was confirmed neuropathologically (Figure 1). A brother had been diagnosed with ALS, with onset at age 54, and the father, who died at age 69, had a dementing illness diagnosed at age 65 and thought to be AD. The father had disappeared one winter day and the body was not discovered until the following spring.

Family 3

AD and ALS were diagnosed in a mother and son, respectively, from a family enrolled in the Newfoundland Alzheimer study (Figure 2). The son with ALS was 37 years of age at the time of diagnosis, which was confirmed at the Montreal Neurological Institute. He presented with a marked nasal type of speech, which progressed fairly rapidly to dysarthria, dysphagia, spastic gait and muscle weakness beginning in the upper extremities. He died nineteen months later. He never became aphasic. There are nine healthy sibs ranging in age from 31 to 46 years. His father died at age 74 of renal failure. His mother (II-5) is 77 with a four-year history of loss of recent memory. The maternal grandmother died at age 54 from tuberculosis, and the grandfather at age 66 with kidney problems.

The proposita (II-7) had been clinically examined by one of us (W.P-P.) and a psychogeriatrician. At age 72, when enrolled in the study, she had a six-year history of decline in cognitive function, a Hachinski score of 0, and a Mini-Mental Status score of 11. Her serum B12 and folate levels, thyroid function tests, and luetic confirmatory tests were normal. CT scan showed a moderate degree of diffuse atrophy. Thus the clinical evidence for AD is strong. She died at age 74 following hospitalization for a fractured hip. There was no autopsy.

Three of the proposita's other sibs have "probable" AD, not confirmed by autopsy. A brother (II-1) had a five-year history of memory loss prior to death at age 70, a sister (II-4) died at age 79 of a myocardial infarction following a four-year history of loss of cognitive function, and another sister (II-8) died at age 66 with a well-documented 10-year history of cognitive impairment having been institutionalized for the last four years of life.

No particular ethnicity was noted in these reported families to suspect any racial predeliction to AD.

Literature Reports

The observation of ALS and AD in two patients, and in a mother and son led to a search for other examples of concurrences of these two conditions. We noted probable or confirmed ALS in three published families with AD. Two of these are in Heston's pedigrees in which all causes of death are noted in a group of Alzheimer families.[7] In Family 10, AD is present in three generations and the proband's father died at age 61 with "progressive muscular atrophy", which is consistent with the diagnosis of ALS, since this description is used in the ICD coding for motor neuron disease. The short course of the illness, 4 years, supports this. The onset of overt AD in two of three family members was below age 60.

In Heston's Family 28, three of eight sibs had inherited AD from the father. It is proposed that a fourth sib with "bulbar paralysis" had ALS rather than "probable multiple sclerosis". In two of four family members the onset of symptoms of AD was below age 60.

The third example is a multi-generational family of Russian-Jewish origin[8] showing autosomal dominant transmission of AD; it was used in the assignment of the FAD (Familial Alzheimer Disease) marker to chromosome 21.[9] A male patient with ALS (III-10) was recorded whose mother did not have AD, but whose grandmother did. Twelve of 38 family members in his generation had AD.

Discussion

We have observed two patients with neuropathologically confirmed AD and ALS. That this concurrence is simply a coincidence cannot be ruled out, but the rarity of ALS (prevalence 1 in 100,000)[10] makes this an unlikely interpretation in Family 1. Family 2, with a sib and father affected with ALS and AD, respectively, is consistent with the hypothesis of an autosomal dominant gene that causes either or both of the two diseases. Alternatively, separate genes for the two diseases could be segregating in the family, and the patient inherited both of them. This is considered unlikely, since ALS is rarely familial (4% of cases)[11] and when it is, it usually shows an autosomal dominant pattern.[12]

In five of the six families there are several members affected with AD suggesting an association of ALS with the genetic form of AD. The Goudsmit family shows autosomal dominant inheritance of the AD gene in four generations[8] (23 affected

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members). Vertical transmission occurred in three generations in another family (Heston's family 10), and in two generations in the other two families (Heston's family 28 and our family 2; four and two affected members, respectively). Only in the Newfoundland family 3 is the autosomal dominant inheritance pattern unsubstantiated, but it cannot be excluded as the parents died at ages 54 and 66.

Could the occurrence of ALS and AD in the same families be coincidental? Among Heston's families the 2 cases of probable ALS are from 243 first-degree relatives over the age of 30, and from the Newfoundland families the single ALS case is from 706 first- and second-degree relatives. The world-wide prevalence of ALS is 1 in 100,000 population,[10] so the presence of even one case in each of three separate study populations of AD seems more than can be attributed to chance. Nevertheless, AD is a relatively common disorder and ALS, although rare, might be expected to occur.

The prevalence of recognized AD has increased dramatically over the past decade, probably because of increased diagnostic attention and the increasing size of our elderly population. If the etiological agent for AD might also cause ALS, a similar increase in the presence of ALS would be expected. A slight upward trend in ALS death rates over time has been observed in the U.S.[10] We have examined the deaths coded as ALS in the Canadian population from 1969 to 1985.[13] In the first half of this time period the rate was 0.91 per 100,000 population, and in the second half 1.29. Increasing neurological and neurophysiological diagnostic sophistication may have resulted in an increase in the diagnosis of ALS, but this would not seem sufficient to account for this degree of concurrence.

The concurrence of familial ALS with dementia reported by Pinsky and colleagues[14] is presumed to be different from that in the present families, since there were no neurofibrillary tangles in the brains of those cases.

In summary, when ALS and AD occur together in a single individual or in a single sibship, environmental factors cannot be ruled out as an explanation of their concurrence, but when the two diseases occur in multigenerational families, a genetic influence is more likely. The pedigrees reported here support the idea of an inherited susceptibility to disease than can be expressed as AD or ALS. In any case the observed association of AD and ALS is unlikely to be coincidental. We encourage further investigation of their concurrence.

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