Amyotrophic Lateral Sclerosis, Parkinson's Disease and Alzheimer's Disease: Phylogenetic Disorders of the Human Neocortex Sharing Many Characteristics

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ABSTRACT: Features common to amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD) are reviewed. Shared epidemiological aspects include an increasing frequency which is proportional for each disease. We draw attention to geographic non-uniform distribution which, for ALS and PD, correlates positively with latitude. Clinical and pathological overlap occurs in the same patients, and in members of the same family. A high early morning plasma cysteine/sulphate ratio possibly related to the development of proteinacious inclusions, as well as ubiquinated neuronal inclusions, characterize ALS, PD and AD. HLA-DR (the human group II major histocompatibility class) staining is marked in ALS, PD and AD and may represent autoimmunity-incited by-products of neuronal degeneration. Based upon demonstrated glutaminergic connections between the neocortex and anterior horn cells, the entorhinal cortex and the basal ganglia we hypothesize that ALS, AD and PD are phylogenetic disturbances of the neocortical cell. The postsynaptic neuron may degenerate secondarily to anterograde effects of deranged glutamate metabolism. Future therapeutic strategies should be directed to agents that decrease transmission induced by excitatory amino-acids.

RÉSUMÉ: Sclérose latérale amyotrophique, maladie de Parkinson et maladie d'Alzheimer: affections phylogéniques du néocortex humain ayant plusieurs caractéristiques communes. Nous revoyons les éléments communs à la sclérose latérale amyotrophique (SLA), la maladie de Parkinson (MP) et la maladie d'Alzheimer (MA). Une fréquence proportionnellement accrue de chacune de ces maladies est l'aspect épidémiologique commun à ces trois maladies. Nous attirons l'attention sur la distribution géographique inégale qui, pour la SLA et la MP, a une corrélation positive avec la latitude. Il peut exister un chevauchement clinique et anatomopathologique chez un même patient et parmi les membres d'une même famille. La SLA, la MP et la MA sont caractérisées par un rapport cystéine/sulphate plasmatique élevé tôt le matin, possiblement relié à la formation d'inclusions protéiniques, ainsi que par des inclusions neuronales ubiquinées. La coloration pour le HLA-DR (la classe majeure d'histocompatibilité humaine de groupe II) est très marquée dans les trois maladies et peut représenter une réaction d'auto-immunité induite par des produits de dégénération neuronale. En nous basant sur l'existence de connections glutaminergiques entre le néocortex et les cellules de la corne antérieure, le cortex entorhinal et les ganglions de la base, nous émettons l'hypothèse que la SLA, la MP et la MA sont des affections de la cellule du néocortex. Le neurone postsynaptique peut dégénérer secondairement à des effets antérogrades de la perturbation du métabolisme du glutamate. À l'avenir, les stratégies thérapeutiques devraient être dirigées vers les agents qui diminuent la transmission induite par les acides aminés excitateurs.

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Feature characteristics of amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD) occur in Jakob-Creutzfelt disease, Shy-Drager syndrome, parkinsonism-dementia-ALS complex of Guam and as a sequel to encephalitis lethargica.[1,2] The incidence of the Guamanian disease has declined dramatically over the last several decades[3] as has any association of ALS, PD or AD with previous encephalitis.[2,4] Outside these situations, ALS, PD and AD also occur in association with each other and, although unusual in the Western World, there has been increasing interest in clinically overt overlap.

Whilst not implying that ALS, PD and AD are the same disease, simply having different manifestations, we suggest that they share important etiopathogenic aspects and mechanisms. A similar idea was proposed almost 20 years ago by Brait et al.:[5] "the concurrence of sporadic parkinsonism and MND could be a

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chance association; most patients with either disease do not have signs of the other. We wish to emphasize, however, that such a subgroup exists and may prove to be more common if clinicians are aware of the syndrome".[5] More recently, others have speculated that ALS, PD and AD are a spectrum of diseases sharing fundamental aspects.[6-10] It has, for example, been postulated that these diseases are characterized by primary loss of the "isodendritic core".[8] This continuous core of overlapping dendritic fields extends from the spinal cord to the diencephalon and includes the anterior horn cells, locus ceruleus and the substantia innominata.[9] Appel,[10] put forward a unifying hypothesis for the causation of ALS, PD and AD which visualized that in each there was lack of a specific neurotrophic hormone which was normally released by the postsynaptic cell and transported retrogradely to exert influence on the presynaptic terminal.

Here we review the various shared aspects of ALS, PD and AD that have emerged in the last two decades. We shall put forward an hypothesis which emphasizes their similarities. If correct, this concept has implications for treatment and prevention.

Epidemiology

The epidemiological characteristics of ALS, PD and AD are summarized in Table 1. In this discussion Alzheimer's disease (AD) refers to both the presenile and senile forms regardless of age of onset. Separation by age of onset is not supported by epidemiological data.[11] In ALS and PD the incidence and prevalence in men is slightly higher than in women. In AD this is true in younger patients but with increasing age there is reversal of the male:female ratio typical of ALS and PD.[11] This may partly reflect the later age of onset of AD and its relation to greater longevity of women compared to men. The age of onset of overt symptoms in ALS and PD is remarkably similar.[11-16] Symptoms in AD start about a decade later. In all three diseases the incidence and prevalence rates are highly age dependent, increasing exponentially with age. Prevalence for PD and AD peak at age 70+ years, about 5-10 years older than for ALS. This is important in the context of clinical overlap. Given that 80% of patients with ALS live less than three years, its younger peak prevalence tends to preclude development of PD or AD in ALS patients and when they do occur together PD or AD almost always precedes ALS.

Young onset disease (under 40 years of age) for ALS, PD and AD is rare accounting for less than 10% of the total.[17-19] In the majority of younger patients the disease tends to run a longer course. This may be due to greater reserve of the neuronal populations involved and is in keeping with environmentally-induced neuronal loss accelerated by aging.[6]

Table 1: Epidemiological Comparisons of ALS, PD and AD

	ALS	PD	AD
Mean Age Onset (years)	59.3	61.9	71.9
Mean Duration of Disease (years)	2.4	10.5	7.3
Incidence/100,000	1.2	21	401
Prevalence/100,000	4.2	300	2,155
Age of Peak Incidence	55-65	70-80	65-75
M:F Ratio	1.61:1	1.13:1	1.1:1*
Familial Occurrence	< 10%	< 10%	< 10%
Twin Studies		Low Concordance	

* Ratio reversed after age 75 years

It has been appreciated for some time that AD is increasing. This trend has recently been confirmed for ALS and PD.[20-23] That the mortality from three "apparently" unrelated diseases is increasing at proportionally much the same rate strongly favours an environmental aetiology. However, it has been generally accepted that the incidence of ALS, PD and AD are uniform throughout the world, which would be unusual for an environmentally-induced disease. Careful scrutiny of epidemiological studies, which have in large part been carried out in North America and Europe, raises the possibility of non-uniformity.[15,24] For example, crude incidence rates for ALS, derived for 13 countries (23 different studies) correlate positively with latitude degrees North (Figure 1). Similar conclusions for prevalence have been reached for PD based upon death rates and also levodopa utilization and sales.[15] Climate, temperature, degree of Westernization and racial differences may all be relevant factors accounting for these geographic differences. Although a relationship between latitude and incidence or prevalence of AD has not thus far been described geographic distribution appears to be heterogeneous.[25]

Clinical Considerations

ALS, PD and AD are diseases of the aging nervous system. Their cardinal features, weakness, paucity of movement and impaired memory are also characteristic of "normal aging".[26] As one grows older many neurological deficits emerge (including: rigidity, stooped posture, graphesthesia, neglect of simultaneous tactile stimuli, snout, grasp and glabella reflexes).[27] Prospective studies are needed to determine if these features may predate overt ALS, PD and AD and to what extent signs typical of one also occur in the others. Also compounding the issue of overlap is the present lack of specific premortem markers allowing for a definitive diagnosis which must largely be based upon clinical skills.

Genetics

Hereditary forms of ALS, PD and AD, account for less than 5%-10% of all cases.[14,16,28-30] In all three diseases, inheritance is autosomal dominant. The onset of symptoms in the hereditary disease is on average 15 years earlier than the sporadic form. Chromosome 21 was implicated in younger persons with hereditary AD several years ago[31] and it is most interesting that the long arm of the same chromosome has recently been identified as the one responsible for hereditary ALS.[32] We would speculate that it too might be involved in hereditary PD. If it turns out that dysfunction of chromosome 21 is a shared feature of hereditary ALS, PD and AD it might equally be implicated in the control of normal neuronal aging and as such would be important in the pathogenesis of the much more common sporadic forms of these diseases. Twin studies in sporadic PD and AD have not shown concordance amongst monozygotic twins or monozygotic as compared to dizygotic twins, leading one to conclude that genetic factors cannot play a prominent role in sporadic PD or AD.[33-38] Twin studies have not been reported in ALS.

Overt Clinical Overlap

Two varieties of clinical overlap are worthy of consideration. One is the "non-Guamanian" patient who has any combination

of ALS, PD or AD and who does not have other diseases, such as Creutzfeld-Jakob disease or progressive supranuclear palsy, which also typically manifest features of PD, AD or ALS. In our own clinic there have been 16 examples of overt clinical overlap out of a total of 176 (9.6%) patients with ALS identified since 1987 (Table 2). This is probably an underestimation since subtle extrapyramidal features may be difficult to appreciate in the presence of marked upper and lower motor neuron deficits due to ALS. This may be true too for the detection of early cognitive impairment in a disease such as ALS which, having such a dismal prognosis, clearly tends to cause depression. A heightened awareness of the "overlap syndrome" may well result in a larger detection rate.

The mean age of the patients at the time of developing initial symptoms of ALS was 69.3 years with the majority being over 70 years. This is about a decade older than the mean age of onset of ALS with AD or PD, suggesting that overt clinical overlap is more common in later onset disease (see Table 1). Seven had dementia and eight had Parkinson's disease preceding the onset of ALS. One patient had both AD and PD.

There is a significantly higher incidence of clinical parkinsonism in AD; it occurs at a rate 7-10 times more frequently than would be expected by chance.[39-42] Pathological changes typical of PD (nigral Lewy body formation, neuronal loss, and gliosis of pigmented nuclei) may occur in more than 20% of AD brains compared to 3-7% of normal brains.[42] Based upon cell counts and immunohistochemical staining for HLA-DR (a human glycoprotein of the group II major histocompatibility class) senescent nigral neuronal loss alone is an incomplete explanation.[42,43] Bradykinesia and rigidity, usually without tremor, are more characteristic of the AD-PD syndrome. Dementia in the combined syndrome is often more severe and progresses at a more rapid rate than is seen in AD alone.[42]

There is also a high prevalence of dementia in PD; estimates vary from 2-80%.[44,45] The issue of dementia in association with PD has become complex and confusing. The concept that the dementia of PD is "subcortical" and that of AD is "cortical" relates not only to the different types of cognitive impairment seen but also to the type of neuronal inclusion (Lewy bodies or senile plaques). This separation is far from specific and at best is

Table 2: AD or PD Overlap in 16 Patients with ALS

M	57	AD	4 mos	M	79	PD	2 yrs	F	83	AD/PD	4 mos
F	61	AD	6 mos	F	71	PD	5 yrs				
F	68	AD	2 yrs	M	75	PD	15 mos				
F	64	AD	18 mos	M	73	PD	10 yrs				
F	55	AD	3 yrs	M	75	PD	2 yrs				
M	77	AD	4 yrs	F	76	PD	12 yrs				
M	68	AD	2 yrs	M	54	PD	6 mos				
				F	72	PD	(sim)				

Interval for developing ALS in patients with AD or PD; (sim = simultaneous onset). This represents 9.6% of 176 patients with ALS seen between 1987-1990.

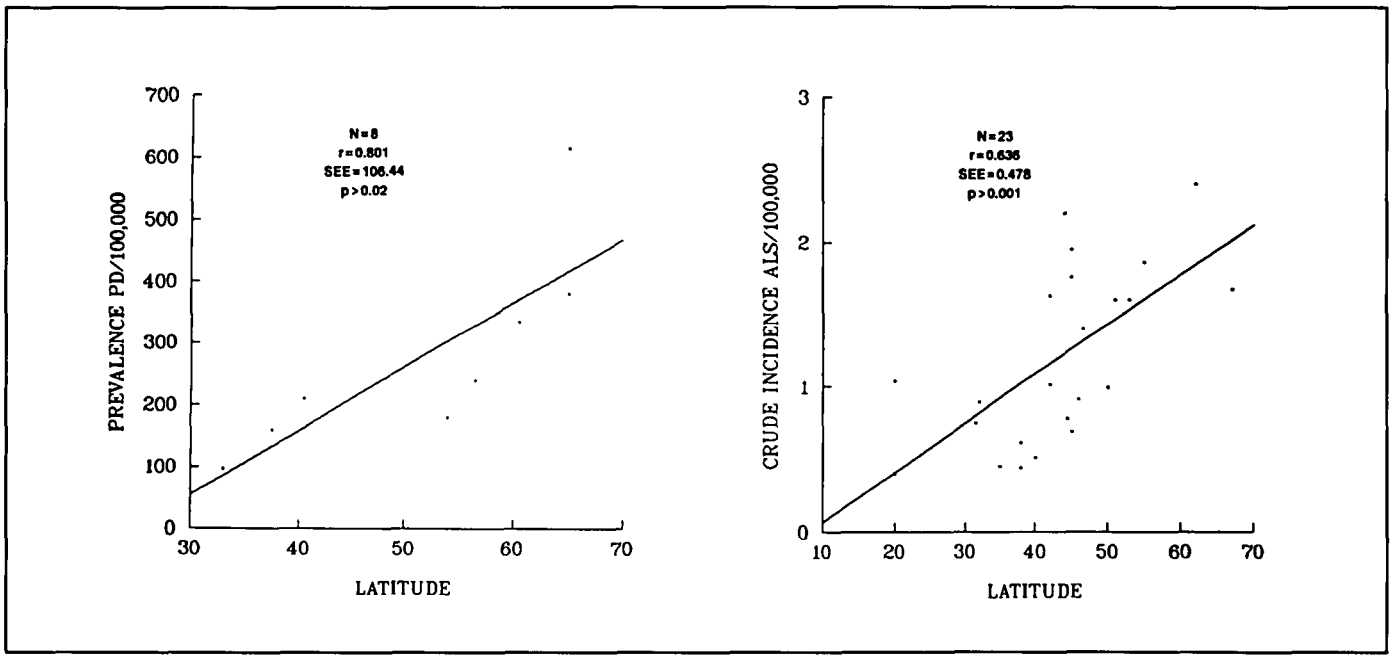

Figure 1 — Relationship between latitude degrees North and prevalence of Parkinson's disease, and crude incidence of ALS. The data for PD were derived from Cuesta JP (ref 15). The ALS data are from 23 studies in 17 different countries.

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an oversimplification.[46,47] In one study in which clinical and pathological data were independently analyzed, 9 (31%) of 29 patients with PD with severe dementia had cortical senile plaques and fibrillary tangles. In another 7 (24%) having mild dementia, 3 had the same pathological changes.[48]

For an excellent discussion on neuronal inclusions in PD the reader is referred to Gibb et al.[47] To summarize, neither the Lewy body, (which is smooth and rounded with an eosinophilic core and pale halo), nor the pale body (which has a uniformly granular texture, fails to show histological staining and lacks a halo), are diagnostic of PD. Lewy bodies may be found diffusely in PD (diffuse Lewy body disease) or dementia without PD.[49]

Nevertheless, several recent reports have suggested that diffuse Lewy bodies in association with dementia constitutes a unique nosological entity differing from AD even though senile plaques and neurofibrillary tangles may also be present.[49-52] The syndrome of DLBD is characterized clinically by: progressive subcortical as well as cortical dementia, psychiatric symptoms, mild extrapyramidal findings with a gait disorder and a burst pattern on EEG. Pathologically there are Lewy bodies in the neocortex, substantia nigra, and substantia innominata. There may be temporal lobe vacuolization. Given available evidence we would argue against the validity of a specific disease entity characterized by diffuse Lewy bodies. The issue has been even further complicated by a recent description of nigral neurofibrillary tangles (with neuronal loss and gliosis) in the absence of Lewy bodies in the four young patients with Parkinson's disease without cognitive impairment.[53]

Both Lewy bodies and senile plaques are being more readily recognized by anti-ubiquitin immunocytochemistry and they frequently occur together. Therefore, it seems almost impossible to ascribe how much the dementia of PD is due to one or the other pathological marker. Whilst it may well be that dementia in PD is heterogeneous it seems difficult to avoid the conclusion that the combination of Lewy bodies and parkinsonism on the one hand and senile plaques, with neurofibrillary tangles and dementia on the other hand, are frequently combined in an overlap of PD and AD.

Overlap in 1st-Degree Relatives and Spouses

Recent studies concur with our own observations that the prevalence of PD and AD is significantly higher in family members with ALS than would be anticipated.[54,55] Similarly, compared to controls there is about a threefold (14:5) risk of developing Parkinson's disease in 1st-degree relatives of patients with AD.[56] Preliminary data from our clinic suggest that there is also a higher than anticipated occurrence of one spouse having ALS if the other has AD or PD. If these observations can be confirmed they would favour some shared environmental risk factors.

Chemical Overlap

Recent studies have shown that patients with ALS, PD or AD have higher early morning plasma cysteine/sulphate ratios than controls (both normal subjects and controls with other diseases).[57] It has been postulated that elevated cysteine might result in toxicity because of high intracellular thiol groups which would disrupt enzyme activity and protein synthesis and conformation.[57] Such events might play a role in the development of proteinaceous accumulations in the form of Lewy bodies (PD), Bunina bodies (ALS) and amyloid protein (AD).

Neurochemical studies have further demonstrated that in both PD and AD there is a reduction in nicotinic receptors and immunoreactivity to corticotropin-releasing factors (CRF) and neuropeptide-Y (NPY). The significance of these observations remain to be elucidated.[58]

Pathological Aspects

Ubiquinated Cytoplasmic Inclusions

Ubiquitin is a highly conserved "heat shock, stress" protein present in all living cells. It is thought to be involved in the ATP-dependent, non-lysosomal degradation of abnormal proteins.[59,60]

Ubiquitinated neuronal inclusions have been described in a variety of conditions. They include: the neurofibrillary tangles of AD, Down's syndrome, and dementia pugilistica,[60] Lewy bodies of PD, Lewy-like bodies in anterior horn cells and motor cortex in ALS, Pick bodies in Pick's disease, Mallory bodies in alcoholic liver disease, astrocytic Rosenthal fibres, and in postencephalitic parkinsonism, as well as normal aging.[60-62] Ubiquitination may simply reflect a non-specific response to the breakdown of neurofilamentous material. However, it is of interest that ubiquinated bodies occur so prominently in ALS, PD and AD and they may indicate that cell death in all three may have a similar mechanism.

Histocompatability Complex Antigens

Despite a considerable body of work, evidence that ALS, PD and AD are primarily the result of disordered immunity remains unsubstantiated. However, "unconventional" disordered immunity cannot be ruled out.[63] Recent studies support the idea that once neuronal degeneration has commenced in ALS, PD and AD, autoimmunity induced by cell products may potentiate and perpetuate the process.[43,64-67] It remains to be determined whether such findings are specific for ALS, PD, and AD, or whether they reflect a more general manifestation of chronic neuronal destruction.

A Unifying Hypothesis

As discussed above, ALS, PD and AD, share several features and from time to time one or more of these diseases occurs in the same person. They are diseases of the human aging nervous system, the impact of which has only been fully realized over the last 120 years. With the single exception of a 25-year-old female baboon, recently described with spontaneous PD,[68] natural or experimental animal models that truly mimic ALS, PD or AD have not been described.

We are proposing that ALS, PD and AD are phylogenetic diseases of the human neocortex whose neurons make monosynaptic connections with the anterior horn cell (ALS), the entorhinal cells of the hippocampus (AD) and the nigrostriatal cells of the basal ganglia (PD). The demise of the postsynaptic cells results from anterograde effects. We further speculate that anterograde degeneration of the postsynaptic cell is largely the result of "neural excitation" initiated by deranged glutaminergic metabolism. The neocortical neurites involved are large, rendering them particularly susceptible to a variety of insults. It is likely that demise of the neocortical cell is due to environmental agent(s) but there may be a genetic contribution and chromosome 21 might prove to be a relevant factor in this regard.

Amyotrophic Lateral Sclerosis

Based upon: 1) phylogenetic evolution of the corticomotoneuronal system, 2) considerable morphological and physiological evidence for monosynaptic connections between the corticomotoneuron and anterior horn cell in man (excluding the occular nuclei and the nucleus of Onufrowicz, which are characteristically spared in ALS), and 3) a lack of a natural or experimental animal model truly mimicking ALS, it has been proposed that this disorder is primarily a disease of the corticomotoneuron.[69] This hypothesis can be modified to incorporate the concept of cell death by excitotoxic aminoacids; the "neuroexcitotoxic hypothesis" in ALS[70,71] or other neurodegenerative disease[72-73] L-glutamate is a demonstrated neurotransmitter of the primate corticomotoneuronal system, including those fibres making direct connection between the motor cortex and the contralateral cervical and lumbar anterior horn cells.[74] In patients with ALS there is deranged glutamatergic metabolism.[70,71]

Alzheimer's Disease

A similar concept can also be applied to AD. The neuropathological markers of AD (neurofibrillary tangles, neuritic plaques and neuronal loss) are prominent and consistent in the entorhinal cortex (especially neurons in layers II and III) and the hippocampus.[75] The entorhinal neurons receive input from widespread cortical areas and give rise to the perforant pathway that terminates in the hippocampal formation. Loss of the entorhinal cells deafferents the hippocampal formation from its main cortical input and it is this that may well underly some, or all, of the cognitive impairment in AD.[76] Glutamate is the major excitatory transmitter of the perforant pathway and has been shown to be markedly reduced in its terminal zone.[77,78] This reduction has recently been confirmed and it has been shown for the first time that neurites associated with senile plaques also contain glutamate. Thus it may be the glutamatergic pyramidal neurons, involved in corticocortical connections, that are preferentially vulnerable in AD.[79]

Parkinson's Disease

In PD, the lack of direct (monosynaptic) glutamatergic connections between the cortex and substantia nigra is clearly different from the situation in ALS and AD. Nevertheless there is growing experimental evidence allowing one to conclude that cortical-excitotoxic (glutamatergic) influences on the basal ganglia are of importance.[80-82] Glutamate dehydrogenase (GDH) levels are considerably reduced in the postmortem putamen of patients with PD.[83] Decreased levels of GDH, by increasing local glutamate concentrations, might exert an excitotoxic effect via NMDA receptors on striatal dopamine nerve terminals,[84,85] and NMDA-receptor antagonists protect against MPTP-induced degeneration of dopamine neurons in rodents.[85,86] More recently NMDA antagonists have been shown to potentiate the beneficial effects of L-dopa administered to monoamine-depleted rats.[87]

Input into the basal ganglia and motor thalamus is derived through glutamatergic, excitatory cortical projections originating over a wide area of cortex.[88,89] Specific cortical areas project (the "input" stage of the basal ganglia) to selected portions of caudate nucleus, putamen and ventral striatum. The "output" nuclei (the internal segment of the globus pallidus, substantia nigra pars reticulata and ventral pallidum) send GABA-mediated, inhibitory projections to the thalamus.[88] There is also an indirect pathway: cortex – putamen (glutamate), putamen – external segment of the globus pallidus (GABA), external pallidum – subthalamic nucleus (GABA) and subthalamic nucleus – substantia nigra (glutamate).[88] There is also evidence for presynaptic localization of glutamate receptors on nigro-striatal terminals suggesting a functional interaction between dopaminergic and excitatory amino acid systems in the striatum.[90]

Our overall hypothesis, if correct, has important therapeutic implications. Excitatory amino acid receptors are classified according to their selective binding of ligands such as NMDA, quisqualate and kainate and it is possible that these excitatory amino acid receptor subtypes are disturbed differently in ALS, PD and AD. The development of suitable (specific) drugs inhibiting release or binding of relevant excitotoxins would be a logical therapeutic and possible protective approach for the future of these neurodegenerative diseases of the aging nervous system.[69,70,86]

References

1. Hudson AJ, Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. Brain 1981; 104: 217-247.
2. Hudson AJ, Rice GPA. Similarities of Guamanian ALS/PD to post-encephalitic parkinsonism/ALS: possible viral cause. Can J Neurol Sci 1990; 17: 427-433.
3. Garruto RM, Yanagihara R, Gajdusek DC. Disappearance of high-incidence amyotrophic lateral sclerosis and parkinsonian-dementia on Guam. Neurology 1985; 35: 193-198.
4. Calne DB, Lees AJ. Late progression of post-encephalitic Parkinson's syndrome. Can J Neurol Sci 1988; 15: 135-138.
5. Brait K, Fahn S, Schwarz GA. Sporadic and familial parkinsonism and motor neuron disease. Neurology 1973; 23: 990-1002.
6. Calne DB, Eisen A, McGeer E, et al. Alzheimer's disease, Parkinson's disease and motorneurone disease: a biotrophic interaction between aging and environment? Lancet 1986; II: 1067-1070.
7. Calne DB, Eisen A. The relationship between Alzheimer's disease, Parkinson's disease and motor neuron disease. Can J Neurol Sci 1989; 16: 547-550.
8. Calne DB, Eisen A. Parkinson's disease, motoneuron disease and Alzheimer's disease: origins and interrelationship. Adv Neurol 1990; 53: 355-360.
9. Rosser MN. Parkinson's disease and Alzheimer's disease as disorders of the isodendritic core. Br Med J 1981; 283: 1588-1590.
10. Appel SH. A unifying hypothesis for the cause of amyotrophic lateral sclerosis, parkinsonism and Alzheimer's disease. Ann Neurol 1981; 10: 499-505.
11. Rocca WA, Amaducci LA, Schoenberg BS. Epidemiology of clinically diagnosed Alzheimer's disease. Ann Neurol 1986; 19: 415-424.
12. Teravainen H, Forgach L, Hietanen M, et al. The age of onset of Parkinson's disease: etiological implications. Can J Neurol Sci 1986; 13: 317-319.
13. Bayles KA. Age of onset of Alzheimer's disease. Arch Neurol 1991; 48: 155-159.
14. Hudson AJ. Amyotrophic lateral sclerosis: clinical evidence for differences in pathogenesis and etiology. *In*: Hudson AJ, ed., Amyotrophic Lateral Sclerosis: Concepts in Pathogenesis and Etiology. Toronto: University of Toronto Press, 1990: 108-143.
15. Cuesta JP. Studies on the prevalence of paralysis agitans by tracer methodology. PhD thesis; Departments of Social Medicine and Endocrinology, Karolinska Institute, Stockholm, Sweden. Huddinge 1986: 113.
16. Rajput AH, Calne D, Lang AE. National Conference on Parkinson's Disease – Conference summary. Can J Neurol Sci 1991; 18: 87-92.

17. Bozek C, Eisen A. Acquired motor neuron disease of the young. Neurology 1985; 25 (Suppl 1): 249.
18. Mukai E, Sakakibara T, Sobue I. The relationship between prognosis and sex and age at onset in amyotrophic lateral sclerosis. Clin Neurol 1984; 24: 679-685.
19. Golbe LI. Young-onset Parkinson's disease: a clinical review. Neurology 1991; 41: 168-173.
20. Lilenfeld DE, Chan E, Ehland J, et al. Rising mortality for mononeuron disease in the USA, 1962-84. Lancet 1989; 1: 810-813.
21. Stallones I, Kasarkis EJ, Stipanowich C, et al. Secular trends in mortality rates from motor neuron disease in Kentucky, 1964-1984. Neuroepidemiology 1989; 8: 68-78.
22. Flaten TP. Rising mortality from mononeuron disease. Lancet 1989; 1: 1018-1019.
23. Lilienfeld DE, Chan E, Ehland J, et al. Two decades of increasing mortality from Parkinson's diseases among US elderly. Arch Neurol 1990; 47: 731-734.
24. Annegers JF, Appel S, Lee JR, et al. Incidence and prevalence of amyotrophic lateral sclerosis in Harris County, Texas, 1985-1988. Arch Neurol 1991; 48: 589-593.
25. Rocca WA, Bonaiuto S, Lippi A, et al. Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: a door-to-door survey in Appignano, Macerata province, Italy. Neurology 1990; 40: 626-631.
26. Calne DB, Calne JS. Normality and disease. Can J Neurol Sci 1988; 15: 3-4.
27. Morris JC, Drazner M, Fulling K, et al. Clinical and pathological aspects of parkinsonism and Alzheimer's disease. Arch Neurol 1989; 46: 651-657.
28. Strong MJ, Hudson AJ, Alvord WG. Familial amyotrophic lateral sclerosis, 1850-1989: a statistical analysis of the world literature. Can J Neurol Sci 1991; 18: 46-58.
29. Fitch N, Backer R, Heller A. The inheritance of Alzheimer's disease: a new interpretation. Ann Neurol 1988; 23: 14-19.
30. Golbe LI. The genetics of Parkinson's disease: a reconsideration. Neurology 1990; 40 (Suppl 3): 7-14.
31. St George-Hyslop P, Tanzi R, Polinsky R, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. Science 1987; 235: 885-890.
32. Siddique T, Figlewicz DA, Pericak-Vance MA. Linkage of a gene causing familial amyotrophic lateral sclerosis to chromosome 21 and evidence for genetic locus heterogeneity. N Engl J Med (in press).
33. Golbe LI, Dilorio G, Bonavita V, et al. A large kindred with autosomal dominant Parkinson's diseases. Ann Neurol 1990; 27: 276-282.
34. Poirier J, Kogan S, Gauthier S. Environment, genetics and idiopathic Parkinson's disease. Can J Neurol Sci 1991; 18: 70-76.
35. Marsden CD. Parkinson's in twins. J Neurol Neurosurg Psychiatry 1987; 50: 105-106.
36. Martila RJ, Kaprio J, Koskenvuo M, et al. Parkinson's in a nationwide twin cohort. Neurology 1988; 38: 1217-1219.
37. Creasey H, Jorm A, Longley W, et al. Monozygotic twins discordant for Alzheimer's disease. Neurology 1989; 39: 1474-1476.
38. Renvoize EB, Mindham RHS, Stewart M, et al. Identical twins discordant for presenile dementia of the Alzheimer type. Br J Psychiatry 1986; 149: 509-512.
39. Galasko D, Kwo-on-Yuen PF, Klauber MR, et al. Neurological findings in Alzheimer's disease and normal aging. Arch Neurol 1990; 47: 625-627.
40. Leverenz J, Sumi SM. Parkinson's disease in patients with Alzheimer's disease. Arch Neurol 1986; 43: 662-664.
41. Ditter SM, Mirra SS. Neuropathological and clinical features of Parkinson's disease in Alzheimer's disease patients. Neurology 1987; 37: 754-760.
42. Boller F, Mizutani T, Roessmann U, et al. Parkinson's disease, dementia and Alzheimer's disease: clinicopathological correlations. Ann Neurol 1980; 7: 329-335.
43. McGeer PL, Itagski S, Akiyama H, et al. Rate of cell death in parkinsonism indicates active neuropathological process. Ann Neurol 1988; 24: 574-576.
44. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 1988; 24: 50-56.
45. Gaspar P, Gray F. Dementia in idiopathic Parkinson's disease: a neuropathological study of 32 cases. Acta Neuopathol 1984; 64: 43-52.
46. Whitehouse PJ. The concept of subcortical and cortical dementia: another look. Ann Neurol 1986; 19: 1-6.
47. Gibb WRG, Scott T, Lees AJ. Neuronal inclusions of Parkinson's disease. Movement Disorders 1991; 6: 2-11.
48. Price DL, Whitehouse PJ, Struble RG. Cellular pathology in Alzheimer's and Parkinson's disease. Trends Neurosci 1986; 9: 29-33.
49. Gibb WR, Mountjoy CQ, Mann DM, et al. A pathological study of the association between Lewy body disease and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1989; 52: 701-708.
50. Lennox G, Lowe JS, Godwin-Austin RB, et al. Diffuse Lewy body disease: an important differential diagnosis in dementia with extrapyramidal features. Prog Clin Biol Res 1989; 317: 121-130.
51. Hansen L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease: a clinical and pathological entity. Neurology 1990; 40: 1-8.
52. Crystal HA, Dickson DW, Lizardi JE, et al. Antemortem diagnosis of diffuse Lewy body disease. Neurology 1990; 40: 1523-1528.
53. Rajput AH, Uitti RJ, Sudhakar S, et al. Parkinsonism and neurofibrillary tangle pathology in pigmented nuclei. Ann Neurol 1989; 25: 602-606.
54. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol 1986; 123: 790-799.
55. Mulder DW, Kurland LT, Offord KP, et al. Familial adult motor neuron disease: amyotrophic lateral sclerosis. Neurology 1986; 36: 511-517.
56. Hofman A, Schulte W, Tanja TA, et al. History of dementia and Parkinson's disease in 1st-degree relatives of patients with Alzheimer's disease. Neurology 1989; 39: 1589-1592.
57. Heafield MT, Fearn S, Steventon GB, et al. Plasma cysteine and sulphate levels in patients with motor neurone, Parkinson's and Alzheimer's disease. Neurosci Lett 1990; 110: 216-220.
58. Whitehouse PJ. Parkinson's diseases and Alzheimer's disease: new neurochemical parallels. Movement Disorders 1989; 4 (Suppl 1): 57-62.
59. Garofalo O, Kennedy PGE, Swash M, et al. Ubiquitin and heat shock protein expression in amyotrophic lateral sclerosis. Neuropathol Appl Neurobiol 1991; 17: 39-45.
60. Dale GE, Leigh PN, Luthert P, et al. Neurofibrillary tangles in dementia pugilistica are unbiquinated. J Neurol Neurosurg Psychiatry 1991; 54: 116-118.
61. Leigh PN, Anderton BH, Dodson A, et al. Ubiquitin deposits in anterior horn cells in motor neuron disease. Neurosci Lett 1988; 93: 197-203.
62. Murayama S, Mori H, Ihara Y, et al. Immunocytochemical and ultrastructural studies of lower motor neurons in amyotrophic lateral sclerosis. Ann Neurol 1990; 27: 137-148.
63. Drachman DB, Kuncl RW. Amyotrophic lateral sclerosis: an unconventional autoimmune disease? Ann Neurol 1989; 26: 269-274.
64. McGeer PL, Itagaki S, Tago H, et al. Reactive microglia in patients with senile dementia of the Alzheimer's type are positive for the histocompatibility glycoprotein HLA-DR. Neurosci Lett 1987; 79: 195-200.
65. McGeer PL, Itagaki S, McGeer EG. Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. Acta Neuropathol 1988; 76: 550-557.
66. Sobel RA, Ames MB. Major histocompatibility complex molecule expression in the human central nervous system: immunohistochemical analysis of 40 patients. J Neuropathol Exp Neurol 1988; 47: 19-28.
67. Lampson LA, Kushner PK, Sobel RA. Major histocompatibility complex antigen expression in the affected tissues in amyotrophic lateral sclerosis. Ann Neurol 1990; 28: 365-372.

68. Moss MB, Saint-Hilaire M, Feldman RG, et al. Spontaneously occurring Parkinson's disease in a nonhuman primate. Ann Neurol 1991; 30: 297.
69. Eisen A, Kim S, Pant B. Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotoneuron? Muscle & Nerve (in press).
70. Plaitakas A, Constantakakis E, Smith J. The neuroexcitotoxic amino acids glutamate and aspartate are altered in spinal cords and brain in amyotrophic lateral sclerosis. Ann Neurol 1988; 24: 446-449.
71. Plaitakis A. Glutamate dysfunction and selective motor neuron degeneration in amyotrophic lateral sclerosis: a hypothesis. Ann Neurol 1990; 28: 3-8.
72. Stone TW, Burton NR. NMDA receptors and ligands in the vertebrate CNS. Prog Neurobiol 1988; 30: 333-368.
73. McDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Rev 1990; 15: 41-70.
74. Young AB, Penney JB, Dauth GW, et al. Glutamate or aspartate as a possible neurotransmitter of cerebral corticofugal fibres in the monkey. Neurology 1983; 33: 1513-1516.
75. Hyman BT, Van Hoesen GW, Damasio AR, et al. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984; 225: 1168-1170.
76. Hyman BT, Van Hoesen GW, Kromer LJ, et al. Perforant pathway changes and the memory impairment of Alzheimer's disease. Ann Neurol 1986; 20: 472-481.
77. Margaros WF, Greenamyre JT, Penney JB. Glutamate dysfunction in Alzheimer's disease: a hypothesis. Trends Neurosci 1987; 10: 65-67.
78. Hyman BT, Van Hoesen GW, Damasio AR. Alzheimer's disease: glutamate depletion in the hippocampal perforant pathway zone. Ann Neurol 1987; 22: 37-40.
79. Kowall NW, Beal MF. Glutamate-, glutaminase-, and taurine-immunoreactive neurons develop neurofibrillary tangles in Alzheimer's disease. Ann Neurol 1991; 29: 162-167.
80. Goldman-Rakic PS, Selmon LD. New frontiers in basal ganglia research. Trends Neurosci 1990; 13: 241-244.
81. Rouzaire-Dubois B, Scarnati E. Pharmacological study of the cortical-induced excitation of subthalamic nucleus neurons in the rat: evidence for amino acids as putative transmitters. Neuroscience 1987; 21: 429-440.
82. Smith Y, Parent A. Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. Brain Res 1988; 453: 353-356.
83. Cedarbaum JM, Sheu KFR, Harding BJ, et al. Deficiency of glutamate dehydrogenase in postmortem brain samples from parkinsonian putamen. Ann Neurol 1990; 28: 111-112.
84. Clow DW, Jhamandas KJ. Characterization of L-glutamate action on the release of endogeneous dopamine from the rat caudate-putamen. J Pharmacol Exp Ther 1989; 248: 722-278.
85. Sonsella PK, Nicklas WJ, Heikkila RE. Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. Science 1989; 244: 398-400.
86. Turski L, Bressler K, Rettig K, et al. Protection of substantia nigra from MPP^+ neurotoxicity by N-methyl-D-aspartate antagonists. Nature 1991; 349: 414-418.
87. Klockgether T, Turski L. NMDA antagonists potentiate antiparkinsonian actions of L-dopa in monoamine-depleted rats. Ann Neurol 1990; 28: 539-546.
88. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neuronal substrates of parallel processing. Trends Neurosci 1990; 13: 266-271.
89. Albin RL, Young AB, Penney JP. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989; 12: 366-375.
90. Carrozza DP, Ferraro TN, Golden GT, et al. Partial characterization of kainic acid-induced striatal dopamine release using *in vivo* microdialysis. Brain Res 1991; 543: 69-76.

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