Amyotrophic Lateral Sclerosis/Parkinsonism/Dementia: Clinico-Pathological Correlations Relevant to Guamanian ALS/PD

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ABSTRACT: In a recent report on the clinical and pathological features of Guamanian ALS/PD and post-encephalitic parkinsonism/ALS a number of similarities were described, notably in the distribution of neurofibrillary tangles throughout the nervous system.[1] In this account additional pathological features which these disorders share (and which differ from classical ALS, Parkinson's and Alzheimer's diseases) are described. These include atrophy of the globus pallidus and the entire substantia nigra, viz. pars compacta and pars reticulata. Moreover, neither Lewy bodies nor senile plaques are features of the Guamanian and post-encephalitic disorders. The significance of these observations and their relationship, more generally, to parkinsonism, ALS and dementia are discussed.

RÉSUMÉ: Sclérose latérale amyotrophique / parkinsonisme / démence : corrélations pertinentes à la SLA/MP de Guam. Un certain nombre de similitudes, particulièrement dans la distribution des amas neurofibrillaires à travers le système nerveux, ont été décrites dans une publication récente sur les manifestations cliniques et anatomopathologiques de la SLA/MP de Guam et le parkinsonisme/SLA post-encéphalitique.[1] Dans ce compte rendu, des manifestations anatomopathologiques supplémentaires communes ont été rapportées (différentes de la SLA classique, des maladies de Parkinson et d'Alzheimer) comprenant l'atrophie du globus pallidus et du locus niger tout entier, à savoir la zona compacta et la zona reticulata. De plus, ni les corps de Lewy ni les plaques séniles ne sont des manifestations des syndromes de Guam et post-encéphalitique. Nous descutons de la signification de ces observations et de leur relation plus générale au parkinsonisme, à la SLA et à la démence.

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The most common clinical expressions of progressive and unremitting injury to motor neuron, nigrostriatal and cortical neuronal systems are classical amyotrophic lateral sclerosis (ALS), Parkinson's disease and Alzheimer's disease. Combined involvement of all three of these systems, in which ALS, parkinsonism and dementia constitute different aspects of the same entity is rare and occurs in the ALS/parkinsonism-dementia complex (ALS/PD) of Guam. A very similar but presently less common and much less familiar combination of findings is found in post-encephalitic parkinsonism/ALS, a sequel to encephalitis lethargica. In a recent account it was shown that there are a number of clinicopathological features that these rare combined neurodegenerative disorders have in common.[1] Moreover, their features are distinct from those by which classical ALS, Parkinson's and Alzheimer's diseases are recognized. In the present report some additional features that are shared by these combined conditions are described.

Guamanian ALS/Parkinsonism-Dementia (ALS/PD)

Guamanian ALS/PD had a high incidence in the post-World War II years which has markedly declined since. Environmental, and especially nutritional, factors have been suspected for some time as contributing to its cause. The parkinsonism in ALS/PD is characterized by rigidity (similar to post-encephalitic parkinsonism/ALS) and a rhythmic but not typically pill-rolling tremor.[1] Dementia is a significant feature and depression, sleep disorders and behaviour disturbances are also common.[2,3] Guamanian ALS is clinically indistinguishable from classical ALS but during the early years following its discovery the disease had a young age of onset and a slightly longer duration.

Post-Encephalitic Parkinsonism/ALS

Encephalitis lethargica was pandemic in the period between 1915 and 1928 and then declined with only very occasional

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reports of cases of encephalitis after 1930, but its sequelae, post-encephalitic parkinsonism/ALS (especially parkinsonism), were observed over the ensuing 2 to 3 decades.[1,4,5] Swine influenza spread over the world at the same time as the encephalitis lethargica pandemic and because of their concurrence the influenza virus has been thought by a number of investigators to be the cause of encephalitis lethargica.[1] However, this is unproven.

When the encephalitis was severe the post-encephalitic disorder tended to follow immediately or within a period of 6 months.[1] When the encephalitis was mild the onset of parkinsonism and ALS was often delayed for years, sometimes for decades. The parkinsonism was rigid in type like Guamanian ALS/PD and although the tremor was very similar it was possibly more pill-rolling in character. Depression, sleep disturbances and emotional instability were common and patients often displayed various tics and oculogyric spasms. Post-encephalitic ALS, like Guamanian ALS, had a younger age of onset and a slightly longer duration than classical sporadic ALS.

Comparison of Clinical Features of ALS, Parkinsonism and Dementia in the Classical, Guamanian and Post-Encephalitic Disorders

Amyotrophic Lateral Sclerosis

The clinical appearance and progression of ALS in Guamanian ALS/PD and post-encephalitic parkinsonism/ALS is the same as in classical ALS.[6] Because lower motor neurons are distributed throughout the entire length of the spinal cord the progress of ALS can be followed as these neurons degenerate and muscles waste. If ALS cases of all types are observed from onset muscular wasting is usually seen to begin focally and to extend and involve adjacent, and eventually, more distant motor neurons. As the disease advances other regions independently show wasting and weakness but the initial appearance is a contiguous spread of the process to involve adjacent motor neurons.

Parkinsonism

The Parkinson features of Guamanian and delayed onset post-encephalitic parkinsonism resemble those of classical Parkinson's disease with minor differences (see above).[1] However, the oculogyric spasms and tics that accompany post-encephalitic parkinsonism have not been described in either ALS/PD or the classical disease. It is difficult to know if parkinsonism in any of its different forms has a truly focal onset and spread within the substantia nigra as in the case of lower motor neuron degeneration in ALS.

Dementia

Dementia is the predominant feature of Alzheimer's disease but dementia also occurs in Parkinson's disease and in Guamanian ALS/PD due, most likely, to similar pathological disruption of Papez circuit (see below). This may begin focally, e.g. entorhinal region. Dementia in post-encephalitic parkinsonism/ALS has not been reported despite very similar emotional, behavioural and pathological features to ALS/PD.

Pathological Comparisons of ALS, Parkinsonism and Dementia in the Classical, Guamanian and Post-Encephalitic Disorders

Amyotrophic Lateral Sclerosis

Pathological examination of the nervous system in classical, Guamanian and post-encephalitic ALS reveals similar upper and lower motor neuron loss. Moreover, Bunina bodies and axonal spheroids are present in both classical and Guamanian disease. These inclusions have not been reported in post-encephalitic ALS but they may not have been sought.[7] The striking difference between classical ALS and Guamanian and post-encephalitic ALS is the presence (and similar distribution) of neurofibrillary tangles in the latter two conditions.[1]

Parkinsonism

In classical Parkinson's disease the globus pallidus is anatomically spared and there is degeneration of the substantia nigra that is most marked in the pars compacta. In Guamanian ALS/PD and post-encephalitic parkinsonism/ALS, in contrast to Parkinson's disease, there is marked neuronal degeneration of the globus pallidus and *both* the pars reticulata and pars com-

Table 1: Pathological Features in Alzheimer's Disease, Parkinson's Disease, ALS/PD and Postencephalitic Parkinsonism/ALS[1,7-9,11-14]

Feature	Alzheimer's Disease	Parkinson's Disease	Guamanian ALS/PD	Postenceph. Parkinson/ALS
Inclusions/Plaques				
(1) neurofibrillary tangles	+	+	+	+
(2) senile plaques	+	+	-	-
(3) granulovacuolar bodies	+	+	+	+
(4) Lewy bodies	-	+	-	-
(5) Pick bodies	-	-	-	-
Neuronal Loss/Gliosis				
(1) substantia nigra	+	+ (pars compacta)	+ (diffuse)	+ (diffuse)
(2) locus ceruleus	+	+	+	+
(3) globus pallidus	-	-	+	+
(4) caudate-putamen	-	-	-	-
(5) hippocampus	+	+	+	+
(6) cortex*	+ (ftp)	+ (f)	+ (ft)	+ (diffuse)**
(7) nucleus basalis of Meynert	+	+	+	+

* f - frontal, t - temporal, p - parietal
** Inflammation observed in acute encephalitis lethargica

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pacta of the substantia nigra (see Table 1). Lewy bodies and senile plaques that are found in classical Parkinson's disease are not features of either ALS/PD or post-encephalitic parkinsonism/ALS. Neurofibrillary tangles and Simchowics bodies are present in all three disorders but neurofibrillary tangles in Guamanian and post-encephalitic parkinsonism have a similar distribution that is distinctly different from both Parkinson's and Alzheimer's disease.[1,7,8,9]

Dementia

Kalus et al have described the selective distribution of neuronal degeneration, amyloid deposits and neurofibillary tangle formation in the presubicular and entorhinal regions of the hippocampus in Alzheimer's disease.[10] Severe damage due to such changes in the hippocampal region, with especially early involvement of the presubicular and entorhinal parts of Papez circuit, may explain the predominance of memory loss in this disease. Dementia that accompanies Guamanian ALS/PD and Parkinson's disease is probably caused by a similar disruption of the anatomical pathways involved in memory storage and recall. As noted by Braak and associates Alzheimer's disease may have focal onset in the entorhinal region with neuronal spread to other sites within the nervous system via Papez circuit.[10]

Summary

A comparison of the similarities and differences between Guamanian ALS/PD and post-encephalitic parkinsonism/ALS are summarized in the table and as follows: Their **similarities** include: (1) a combination of ALS and parkinsonism, (2) a declining incidence, (3) earlier onset and longer duration than the classical disease, (4) parkinsonism that is predominantly rigid in type, (5) emotional and personality disorder, (6) similar distribution of neurofibillary tangles, (7) atrophy of the globus pallidus and whole substantia nigra, and (8) absence of senile plaques and Lewy bodies. The **differences** are: (1) the presence of oculogyric crises and tics in post-encephalitic parkinsonism/ALS but absent in ALS/PD, (2) dementia not described in post-encephalitic parkinsonism/ALS despite similarity of emotional and behavioural disturbances and extent of pathological changes to ALS/PD, and (3) encephalitis not described on Guam (to our knowledge) prior to the onset ALS/PD. Thus, there are significant similarities between post-encephalitic parkinsonism/ALS and Guamanian ALS/PD with, nevertheless, some clinical differences. The latter may be related to the severity of the encephalitis and interval to onset of post-encephalitic sequelae.

The possible role of the influenza or similar virus, especially as a persistent infection that is prone to intracellular mutation, in the etiology of both disorders has been previously discussed.[1] In this context the Chamorro population of Guam may have been especially vulnerable due to their relative genetic isolation.[15]

References

1. 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.
2. Hirano A, Kurland LT, Krooth RS, et al. Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. Brain 1961; 84: 642-661.
3. Hirano A, Malamud N, Kurland LT. Parkinsonism-dementia complex, endemic disease on the island of Guam. II. Pathological features. Brain 1961; 84: 662-679.
4. Matheson Commission. Epidemic encephalitis; etiology, epidemiology, treatment. New York: Columbia University Press, 1929; 179-399.
5. von Economo C. Encephalitis lethargica: its sequelae and treatment. London: Oxford University Press, 1931.
6. 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.
7. Hirano A, Hirano M, Dembitzer HM. Pathological variations and extent of the disease process in amyotrophic lateral sclerosis. *In:* Hudson AJ, ed. Amyotrophic Lateral Sclerosis: Concepts in Pathogenesis and Etiology. Toronto: University of Toronto Press, 1990; 166-192.
8. Hirano A, Zimmerman HM. Alzheimer's neurofibrillary changes: a topographic study. Arch Neurol 1962; 7: 227-242.
9. Alvord EC, Forno LS. Pathology. *In:* Koller WC, ed. Handbook of Parkinson's Disease. New York: Marcel Dekker, Inc., 1987; 209-236.
10. Kalus P, Braak H, Braak E, et al. The presubicular region in Alzheimer's disease: topography of amyloid deposits and neurofibrillary changes. Brain Res 1989; 494: 198-203.
11. Pakkenberg H, Bottcher J. Corpus striatum in paralysis agitans and perphenazine-injected rats. *In:* McDowell FH, Barbeau A, ed. Second Canadian-American Conference on Parkinson's Disease. Advances in Neurology. New York: Raven Press, 1974; 5: 203-209.
12. Greenfield JG, Bosanquet FD. The brain-stem lesions in parkinsonism. J Neurol Neurosurg Psychiatry. 1953; 16: 213-226.
13. Heyman A, Wikinson WE, Hurwitz BJ, et al. Alzheimer's disease: genetic aspects and associated clinical disorders. Ann Neurol 1983; 14: 507-515.
14. Ditter SM, Mirra SS. Neuropathologic and clinical features of Parkinson's disease in Alzheimer's disease patients. Neurology 1987; 37: 754-760.
15. Maurizi CP. Was a neurovirulent influenza virus the cause of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam? Medical Hypotheses 1987; 23: 325-326.