Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier
ELSEVIER
1353-8020(95)00016-X
Parkinsonism & Related Disorders Vol. 1, No. 2, pp. 65–66, 1995
Elsevier Science Ltd
Printed in Great Britain
1353-8020/95 $9.50 + 0.00

Editorial
The Etiology of Idiopathic Parkinsonism

The possibility of an infectious process being important in the etiology of idiopathic parkinsonism (Parkinson's disease) has been contemplated for many years. Three decades ago it was hypothesized that the incidence of parkinsonism would wane with the passage of time [1]. This hypothesis stemmed from speculation that a substantial proportion of parkinsonian cases resulted from the epidemic of encephalitis lethargica (von Economo encephalitis) earlier this century. However, such a decrease in the incidence of parkinsonism never occurred. In this issue Lin *et al.* report an instance of apparent post- or para-infectious parkinsonism (pp 67–72). Their case is novel in that the patient showed transient parkinsonism unaccompanied by features suggestive of encephalitis lethargica and unassociated with other known causes of parkinsonism. Additionally, a transient T2-weighted high intensity MRI signal in the substantia nigra was documented at the peak of severity of parkinsonism. While it is conceivable that the individual described had underlying idiopathic parkinsonism, with symptoms being merely transiently unmasked by her post-infectious state, this seems unlikely. After most of her symptoms cleared, PET results with fluorodopa and raclopride continued to be consistent with idiopathic parkinsonism. This finding is in contrast to nearly all other instances of secondary parkinsonism which fail to show the disparity in loss of fluorodopa uptake between caudate and putamen (putamen being more severely affected with concomitant increase in raclopride binding).

One may speculate that certain events, such as those described by Lin *et al.*, may cause an asymptomatic substrate which in time will manifest again as idiopathic parkinsonism. While toxic exposures causing parkinsonism have been reported (MPTP, cyanide, lacquer thinner, n-hexane, hydrocarbons, methanol, carbon disulfide, etc.), other transient parkinsonian states have also been reported to follow viral encephalitic infections, including measles [2], Japanese B [3,4], and Western equine [5]. Instances of MRI abnormalities in the substantia nigra and elsewhere have also been documented in patients developing parkinsonism following Japanese encephalitis [6]. Recent studies with a neurovirulent strain of influenza A (WSN) have demonstrated selectivity for the ventral substantia nigra and hippocampus in mice [7] providing further data suggesting a link between specific viral infection and parkinsonism. Case-controlled surveys in humans have generally failed to identify a higher incidence of obvious viral exposure in idiopathic parkinsonism [8,9], although a higher incidence of Spanish flu during childhood has been reported [10] and one cerebrospinal fluid study reported a greater than expected frequency of antibodies to coronavirus in Parkinson's disease patients [11]. The Lewy body, considered by some to be a dynamic region of the neuron important in degrading unwanted proteins, has long been thought to be suggestive of viral infection. Additionally, recent immunohistochemical measures of alpha-interferon and its induced protein, MxA, have shown this protein to be found in Lewy bodies from Parkinson's disease brains, further implying the possibility of viral infection [12]

The possibility of non-viral infections being important in the etiology of parkinsonim is also worthy of study. Kohbata and Beaman [13] reported a levodopa responsive movement disorder in mice caused by *Nocardia asteroides*. Affected animals recovered from an initial dose of *N. asteroides* and later developed an involuntary movement disorder which was alleviated with levodopa therapy. Pathological studies showed loss of Nissl substance in the substantia nigra and reduced staining for tyrosine hydroxylase. Hyaline intracytoplasmic inclusion ('Lewy body-like') bodies were also identified. In human studies, seropositivity for *Nocardia* has been no more frequent in idiopathic parkinsonism than controls [14]. It seems unlikely that Nocardial infection causes parkinsonism. Nevertheless, evaluative studies like those reported by Lin *et al.* are useful in expanding knowledge of potential causes of parkinsonism and fostering etiological speculation.

REFERENCES

1. Poskanzer DC, Schwab RS. Cohort analysis of Parkinson's syndrome: evidence for a single etiology related to sub-clinical infection about 1920. *J. Chron. Dis.* 1963; **16:** 961–973.
2. Sasco AJ, Paffenberger RS Jr. Measles infection and Parkinson's disease. *Am. J. Epidemiol.* 1985; **122:** 1017–1031.

Goto A. A follow-up study of Japanese B encephalitis. *Psychiat. Neurol. Jpn.* 1962; **64:** 236–266.
Shoji H, Watanabe M, Itoh S, Kuwahara H, Hattori F. Japanese encephalitis and parkinsonism. *J. Neurology* 1993; **240:** 59–60.
Mulder DW, Parrott M, Thaler M. Sequelae of Western equine encephalitis. *Neurology* 1951; **1:** 318–327.
Shoji H, Murakami T, Murai I, *et al.* A follow-up study by CT and MRI in 3 cases of Japanese encephalitis. *Neuroradiology* 1990; **32:** 215–219.
Takahashi M, Yamada T, Nakajima S, Nakajima K, Yamamoto T, Okada H. The substantia nigra is a major target for neurovirulent influenza A virus. *J. Exp. Med.* (in press).
Sadie MJ, Sutherland JM, Doherty RL. Encephalitis in eitology of parkinsonism in Australia. *Arch. Neurology* 1965; **12:** 240–245.
Elizan TS, Madden DL, Noble GR, et al. Viral antibodies in serum and CSF of Parkinsonian patients and controls. *Arch. Neurology* 1979; **36:** 529–534.
Treves TA, Wechsler M, Rabey JM, Korczyn AD. Risk factors for Parkinson's diease: case–control study with temporal approach. *Neurology* 1991; **41**(suppl 1): 371.
11. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov. Disord.* 1992; **7:** 153–158.
12. Yamada T, Horisberger MA, Kawaguchi N, Moroo I, Toyoda T. Immunohistochemistry using antibodies to alpha-interferon and its induced protein, MxA, in Alzheimer's and Parkinson's disease brain tissues. *Neurosci. Lett.* 1995; **181:** 61–64.
13. Kohbata S, Beaman BL. L-Dopa-responsive movement disorder caused by Nocardia asteroides localized in the brains of mice. *Infect Immunology* 1991; **59:** 181–191.
14. Kohbata S, Shimokawa K. Circulating antibody to Nocardia in the serum of patients with Parkinson's disease. In: Narabayashi H, Nagatsu T, Yanagisawa N, Mizuno Y, eds. *Parkinson's Disease: From Basic Research to Treatment.* 60th Edn. New York: Ravens Press, 1993: 355–357.

RYAN J. UITTI
Mayo Clinic, Jacksonville