ARTICLE IN PRESS

Parkinsonism and Related Disorders xxx (2017) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The 200-year journey of Parkinson disease: Reflecting on the past and looking towards the future

Stanley Fahn

Columbia University College of Physicians and Surgeons, 710 West 168th Street, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 15 July 2017
Accepted 20 July 2017

Keywords:
Pathology
Substantia nigra
Lewy bodies
L-dopa
Levodopa
Dopamine
Genetics
Alpha-synuclein
Rogue protein
Deep brain stimulation

ABSTRACT

It took almost 100 years before a meaningful advance occurred in any basic science understanding of Parkinson disease (PD) following James Parkinson's description in 1817. The Lewy body was described in 1912, and the substantia nigra was found to be depigmented with neuronal loss and gliosis in 1919. The link between dopamine and PD began in 1957, 140 years after Parkinson's *Essay*. Arvid Carlsson and Oleh Hornykiewicz were the major pioneers. The revolutionary therapeutic breakthrough was the introduction of high dosage levodopa therapy by George Cotzias in 1967.

Following 40 years of the dopa/dopamine era, we have entered the era of alpha-synuclein, the protein present in Lewy bodies. Heiko Braak found that alpha-synuclein accumulates initially in the olfactory system and lower brainstem and then travels in an anatomic pattern to involve other regions of the brain and thereby cause progressive symptoms. Alpha-synuclein was somehow converted to a rogue protein. Where this originates and how it is propagated are under intense investigation.

At the same time that the alpha-synuclein era was developing, clinical advances took place by recognizing PD as hosting a wide variety of nonmotor features with eventual cognitive impairment in many. Therapeutics has also evolved. Although the most effective therapy for the motor features remains levodopa, surgical approaches and drugs for nonmotor problems continue to expand our ability to treat people with PD. We can expect therapeutic advances in neuroprotection as the basic science discoveries uncovered in the alpha-synuclein era are translated into effective treatments.

© 2017 Published by Elsevier Ltd.

1. The first 140 years

James Parkinson's *An Essay on the Shaking Palsy* published 200 years ago characterized predominantly the motor symptoms of the disease now bearing his name [1]. Parkinson mentioned the insidious onset and slow progression over time, and he mentioned a couple of nonmotor features ("sleep becomes disturbed" and "torpid bowels") but he missed dementia ("the senses and intellects being uninjured"), which is now recognized as a late feature in the disease. Advances in understanding the full clinical spectrum, pathology, biochemistry, physiology, etiology and pathogenesis of Parkinson disease (PD) were slow in coming. It has only been in the last 60 years that the scientific basis of PD has been biochemically defined. These advances in the etiology and pathogenesis of PD are happening at an increasingly rapid pace in the last two decades.

1.1. Pathology of PD

It was not until 1895 that the substantia nigra was suggested as being affected in PD [2], based on a case report by Blocq and Marinesco [3] of a tuberculoma in that site that was associated with hemiparkinsonian tremor. For his doctoral thesis, Tretiakoff [4,5] studied the substantia nigra in nine cases of PD, one case of hemiparkinsonism, and three cases of postencephalitic parkinsonism, finding lesions in this nucleus in all cases. With the hemiparkinsonian case Tretiakoff found a lesion in the nigra on the opposite side, concluding that the nucleus served the motor activity on the contralateral side of the body. The substantia nigra, so named because of its normal content of neuromelanin pigment, was noted to show depigmentation, loss of nerve cells, and gliosis. These findings remain the histopathologic features of the disease. In his study, Tretiakoff also confirmed the earlier observations of Lewy [6,7] who had discovered the presence of cytoplasmic inclusions in PD, and Tretiakoff named them Lewy bodies. Lewy had described the inclusions in the substantia innominata and in the

E-mail address: sf1@columbia.edu.

http://dx.doi.org/10.1016/j.parkreldis.2017.07.020
1353-8020/© 2017 Published by Elsevier Ltd.

Please cite this article in press as: S. Fahn, The 200-year journey of Parkinson disease: Reflecting on the past and looking towards the future, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.07.020

dorsal nucleus of the vagus, and not in the substantia nigra. Even in Lewy's subsequent work, he doubted the importance of the substantia nigra, and instead suspected that PD pathology originated in the globus pallidus [8].

Over the next several decades, there was debate as to the most consistent pathology in PD between the pallidum and the nigra. It was finally the conclusive paper by Greenfield and Bosanquet [9] confirming the substantia nigra as the major site of pathology in 1953 that put the matter to rest.

1.2. The place of akinesia in the clinical spectrum of PD

In his "Essay" Parkinson described almost all of the motor features of PD that we recognize today [1]. However, he did not mention "akinesia, bradykinesia or hypokinesia" (used here collectively as akinesia) nor "freezing of gait." Recognition and development of the term "akinesia" came about slowly. Charcot, in his Tuesday Lessons of 1888 related slowness to rigidity and specifically excluded weakness as a cause [10]. Gowers in 1893 [11] described PD as consisting of tremor, weakness, rigidity, flexed posture and short steps, with slowness due in part to rigidity. Oppenheim in 1911 [12] mentioned that impairment and retardation of active movements might occur in the absence of rigidity. He did not relate it to weakness. Wechsler [13] in the 1932 edition of his textbook commented about the special difficulty of initiation of movement as a feature of slowness.

The terms "akinesia, akinesis, and hypokinesia" were at last used by Wilson [14] in his large neurology opus of 1940. Under these terminologies, he related the masked facies, the unblinking eyes, the poverty of movement, and the patient sitting immobile. Schwab, England and Peterson [15] devoted an entire paper in 1959 to the subject of akinesia, which by this time was firmly established as the "lessened muscular power" mentioned by Parkinson. Within the definition of akinesia, these authors mentioned fatigue, decrementing amplitude of movements, difficulty shifting to other contraction patterns, apathy, inability to complete actions, difficulty initiating an act, and the ability to reach normal movement briefly under sudden motivation. Furthermore, they described the difficulty for a patient with PD to execute two motor events simultaneously, all under the rubric of akinesia. In his review of akinesia, Fahn [16] mentioned that Narabayashi [17] coined the term "pure akinesia without rigidity" when describing patients who presented with freezing of gait, today more commonly called primary freezing gait syndrome. Fahn [16] pointed out that akinesia and freezing of gait are two separate, distinctive motor phenomena.

1.3. Treatment

In the first 140 years after Parkinson's Essay, the antimuscarinic drugs were well established as the main medical treatment for PD [18], and stereotactic neurosurgery was beginning to become a major treatment in the 1950's and '60's with Irving Cooper being surgery's main proponent [19]. Around 1867, Charcot found solanaceous alkaloids to be somewhat helpful [20], and these became the accepted and popular therapy for the next 75 years. When basic scientists discovered that these alkaloids had central antimuscarinic activity, pharmaceutical chemists developed synthetic chemical agents that were equally effective, with possibly less adverse effects. Around 1950 these synthetic drugs became the standard medical therapy for PD and were not supplanted until Cotzias showed the remarkable benefit from levodopa [21].

2. The next 40 years – the dopamine era

2.1. Biochemistry of PD

In 1957, Carlsson and colleagues [22] performed a simple, elegant experiment showing that L-dopa, the precursor of catecholamines, reversed the reserpine-induced parkinsonian state in rabbits, while the precursor of serotonin, L-5-hydroxytryptophan, did not. L-dopa is the precursor to dopamine, norepinephrine and epinephrine, and at that time, it was thought that dopamine did not have an independent function but served solely as the immediate precursor of norepinephrine. In 1958, after he developed a method for its chemical assay, Carlsson determined that dopamine was present in brain [23]. By the following year, the regional distribution of dopamine was mapped out in brain in both animals [24] and in humans [25]. In October 1958, in his presentation at the International Catecholamine Symposium, Carlsson [26] suggested that PD was related to brain dopamine. In 1960, Hornykiewicz obtained postmortem human brains and measured dopamine and norepinephrine, showing a neostriatal dopamine deficiency in both PD and postencephalitic parkinsonism [27,28].

How PD pathology in the substantia nigra can be associated with dopamine loss in the striatum remained to be explained. With the development of fluorescence histochemistry, a number of Swedish scientists were able to visualize the cellular localization of the biogenic amines. The cell bodies were localized to several nuclei in the brain stem, and their axons ascended to innervate regions in the cerebral hemispheres [29]. The dopamine-containing cell bodies in the pars compacta of the nigra sent their axons to terminate in the caudate and putamen. Experimental lesions in the primate substantia nigra resulted in a corresponding loss of striatal dopamine [30].

Thus began the era of the biochemical understanding of parkinsonism and the role of dopamine in brain. Ultimately, these discoveries let to trials of levodopa in patients with PD and other forms of parkinsonism, but without remarkable success until the spectacular results of Cotzias using high dosage levodopa [21,31]. Carlsson's contributions eventually led to his being awarded the Nobel Prize in Physiology and Medicine in 2000 [32].

2.2. Treatment in the dopamine era

Levodopa became the major therapeutic weapon against the motor features of PD during this period. Levodopa is particularly effective in reducing the major motoric symptoms in the early stages of the disease – rigidity, bradykinesia and tremor. Tremor can be resistant in a substantial minority of patients. As PD worsens over time, other motor features commonly develop – flexed posture, imbalance (loss of postural reflexes) and freezing of gait. These advanced-state motor problems are largely resistant to levodopa and other dopaminergic agents, which were developed during this dopamine era and are used in place of levodopa and as adjunctive medications to levodopa. Levodopa remains the most effective dopaminergic drug but is not without adverse effects – both motor and nonmotor. The former are largely dyskinesias and fluctuations of response. Deep brain stimulation was developed during this era and has been quite effective in mitigating these motor complications [33]. Nonmotor complications of levodopa are often dose limiting and include orthostatic hypotension, excessive daytime sleepiness, hallucinations and paranoid psychosis. There is continuing development of new pharmacologic agents and other formulations of delivery of levodopa to help overcome some of the problems caused by levodopa. The Dopamine Era continues, and dopaminergic therapy will likely not be supplanted until effective neuroprotective therapy is developed.

Please cite this article in press as: S. Fahn, The 200-year journey of Parkinson disease: Reflecting on the past and looking towards the future, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.07.020

Download English Version:

https://daneshyari.com/en/article/8285600

Download Persian Version:

https://daneshyari.com/article/8285600

Daneshyari.com