E D I T O R I A L / U V O D N I K

UDC: 616.858-02/-08
DOI: 10.2298/VSP1604303M

Parkinson's disease – the hardship at old age

Parkinsonova bolest – tegoba poznih godina

Marija Mučibabić, Gerard W. Canters, Thijs J. Aartsma

Leiden Institute of Physics, Leiden University, Leiden, The Netherlands

Within the recent millennia of turbulent human history frequent fatal diseases ravaged the world. It is estimated, for example, that severe pestilence in Athens in 430–426 BCE that occurred as the consequence of huge overcrowding in the city and insanitary conditions wiped out a third of its population. No less severe was the disease in Constantinople and throughout the Byzantine Empire in 541–544 AD. Medieval Europe also used to be devastated and decimated by frequent outbreaks of infections and contagious diseases, very often 'travelling' from the Far East along the old trade routes. The 'Black Death' hit Europe in 1347–1353 AD not only killing between a third to a half of the European population [1] but also causing economic rage unknown before. The rapid industrialization in the 19th century contributed to the spread of cholera and typhoid. It also emphasized the importance of public health and sanitary conditions. The First World War, 1918–1919, was followed by the 'Spanish flu', a pandemic that killed 50 million people, more than in the War itself.

In modern times human life style changed, hygiene improved tremendously and the development of antibiotics, as well as vaccines brought about breakthroughs in treating infectious diseases. Prolonged lifespans in modern society brought an increase in non-infectious diseases, where cancer, cardiovascular and neurodegenerative diseases took the lead. The number of people with neurodegenerative diseases increases steadily, and no proper therapeutical treatment is available yet. Parkinson's disease follows Alzheimer's disease on the list of most common neurodegenerative diseases [2] and affects approximately 6.3 million people worldwide.

James Parkinson was the first to define the manifestation of shaking palsy described in his, now historical, paper "An essay on the shaking palsy'' almost two centuries ago [3]. He examined three men and observed another three on the streets of London. They all shared symptoms as rest tremor, weakened muscular power, anomalous torso posture and dynamic gait. Parkinson clearly emphasized the difference between the early and the later stages of shaking palsy together with the need for repeated observation over an extended period of time to understand the nature of the disorder. In the 19th century Jean-Martin Charot observed non-tremulous forms of the disease and referred to it as Parkinson's disease [4]. In 1912 Fritz Heinrich Lewy investigated by light microscopy the brain sections of 25 Parkinson's disease patients and later on brain sections of 60 more patients. He identified the abnormal inclusions in nerve cell bodies to be a hallmark of the disease. They were named Lewy bodies after him by Konstantin Nikolaevich Tretiakoff who found similar deposits in the *substantia nigra* [5]. Thanks to Carlsson and his coworkers dopamine was discovered as a putative neurotransmitter [6]. Just a few years after it was discovered by Enringer and Hornykiewicz that Parkinson's disease patients shared a decreased concentration of dopamine in the striatum [5], and the first trials of levodopa, a precursor of dopamine, were started in Parkinson's disease patients [7] to increase dopamine levels in their brains. It resulted in the most potent drug so far for controlling the symptoms of Parkinson's disease, and the Nobel Prize in Medicine was awarded to Arvid Carlsson, Paul Greengard, and Eric R. Kandel in 2000 for their discoveries concerning the role of dopamine in signal transduction in the nervous system.

Due to the lack of laboratory test for Parkinson's disease, it is still diagnosed based on clinical observations. The acronym TRAP is used for the four major signs of Parkinson's disease and it stands for tremor at rest, rigidity, akinesia (bradykinesia) and postural instability [8]. These signs of the disease are associated with primary motor symptoms including dynamic gait, micrographia and others. Next to motor symptoms there are equally important non-motor symptoms such as cognitive impairment, apathy, sleep disorders, etc (Table 1). To monitor the impact of Parkinson's disease there was a need for a standardized scale for a wide

Correspondence to: Marija Mučibabić, Leiden Institute of Physics, Leiden University, Niels Bohrweg 2, 2333 CA Leiden, The Netherlands. E-mail: mucibabic@physics.leidenuniv.nl

Table 1

Symptoms in patients with Parkinson's disease

Motor symptoms	Non-motor symptoms
Tremor at rest, rigidity, bradykinesia, postural instability	Cognitive impairment, bradyphrenia, fatigue, anhedonia, paraesthesia
Dynamic gait, micrographia, trouble turning in bed, history of falls	Depression, apathy
Hypomimia, dysarthria, dysphagia, sialorrhoea	Sensory symptoms
Blepharospasm, dystonia, scoliosis, striatal deformity	Sleep disorders

range of parameters. Widely used nowadays, the Unified Parkinson's disease Rating Scale includes four parts. The first part of the scale comprises non-motor aspects, the second covers daily activities, the third one addresses motor symptoms and the fourth possible complications of prescribed therapy [9]. The disease develops not only in the central, but also in the peripheral and the enteric nervous system [10]. When the disease is diagnosed, approximately 70% striatum dopamine has already been depleted and it advances in time [11]. In the advanced stage of Parkinson's disease most of the dopaminergic neurons are lost, concomitant with significant cell death during the process [12]. Together with dopaminergic cells, choline neurons present in the dorsal vagal nucleus degenerate [13].

Medical treatment mostly involves levodopa, so far the most potent drug for controlling disease symptoms. Next to levodopa, catechol-o-methyl-transferase inhibitors, dopamine agonists and nondopaminergic therapy are applied [14]. Deep brain stimulation and the transplantation of nigral neurons [15] are alternatives in severe cases. All the above-listed approaches to the treatment of Parkinson's disease only control the symptoms, while targeting the underlying cause would be the most desirable solution to halt the development of the disease and to provide a cure. To be able to treat the cause of the disease, it is necessary to understand the molecular mechanism of the disease.

One of the first steps in genetic understanding of this complicated neurodegenerative disease began with the identification of a missense mutation in the gene coding for a small protein, α-synuclein that causes a rare form of Parkinson's disease [16]. Lewy bodies and Lewy neurites were both found to be immunoreactive for α-synuclein [17]. In fact, electron microscopy images showed that Lewy bodies and Lewy neurites are largely composed of 200–600 nm long α-synuclein filaments [18]. These findings brought α-synuclein in the spotlight of the scientific community. The small, 14.5 kDa protein, α-synuclein, is mostly present in the human brain, but is also found in the heart and muscles. It belongs to the group of intrinsically disordered proteins that are known to cling together and form aggregates. They are associated with a number of diseases, most of which are neurodegenerative [19] (Table 2).

Table 2

Intrinsically disordered proteins associated with human diseases

Protein/peptide	Disease(s)	Polypeptide length (number of amino acid residues)	Protein/peptide structure
α-synuclein	Parkinsons's disease Synucleopathies Dementia with Lewy body Multiple system atrophy Lewy body variant of Alzheimer's disease	140	Intrinsically disordered
Amyloid-β peptide	Alzheimer's disease	37–43	Intrinsically disordered
Huntingtin fragments	Huntington's disease	Variable	Mostly intrinsically disordered
Amylin	Type II diabetes	37	Intrinsically disordered
TDP43	Amyotrophic lateral sclerosis	414	Intrinsically disordered
Prion protein	Prion disease Creutzfeld-Jacob disease Bovine spongiform encephalopathy	231	Intrinsically disordered and α-helical

These diseases all correlate with the formation of inter- and intracellular inclusions made of insoluble amyloid fibrillar aggregates. The structures of these amyloids are very similar, although they may be composed of proteins with very different functionality. Amyloids are fibrillar aggregates with a length of up to a few microns, which are stabilized by a characteristic cross-β structure which plays a key role in the interaction between adjacent proteins within the fibrils [20].

A detailed characterization of the mechanism of α-synuclein aggregation, fibrillization and toxicity is crucial to

unravel the pathology of Parkinson's disease at the molecular level. So far the relevant processes during α-synuclein aggregation can be classified into three groups: processes that increase the number of aggregates such as nucleation and fragmentation, processes that increase the size of already formed aggregates, *ie,* the growth process, and the opposite processes that decrease the size and the number of aggregates like dissociation and/or degradation. Morphological heterogeneity of the species formed during the aggregation was studied by atomic force microscopy [21] and electron microscopy. In recent years, optical techniques [22] have been applied to study the aggregation of α-synuclein. On the other hand, many potential inhibitors were identified to inhibit the aggregation process [23, 24], but their precise mechanism remains to be unraveled.

The huge effort invested in the research of Parkinson's disease resulted in well-defined symptoms of the disease, potent therapeutics of these symptoms, and deeper understanding of the molecular mechanisms behind the disease. Nevertheless important questions remain to be answered in the coming years before a cure can be developed.

R E F E R E N C E S

1. *Haensch S, Bianucci R, Signoli M, Rajerison M, Schultz M, Kacki S,* et al. Distinct Clones of *Yersinia pestis* Caused the Black Death. PloS Pathog 2010; 6(10): e1001134. doi:10.1371/journal.ppat.1001134
2. *de Lau LM, Breteler MM.* Epidemiology of Parkinson's disease. Lancet Neurol 2006; 5(6): 525−35.
3. *Parkinson J.* An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002; 14(2): 223−36; discussion 222.
4. *Kempster PA, Hurwitz B, Lees AJ.* A new look at James Parkinson's Essay on the Shaking Palsy. Neurology 2007; 69(5): 482−5.
5. *Goedert M, Spillantini MG, Del Tredici K, Braak H.* 100 years of Lewy pathology. Nat Rev Neurol 2013; 9(1): 13−24.
6. *Björklund A, Dunnett SB.* Dopamine neuron systems in the brain: an update. Trends Neurosci 2007; 30(5): 194−202.
7. *Birkmayer W, Hornykiewicz O.* The effect of l-3,4-dihydroxyphenylalanine (=DOPA) on akinesia in parkinsonism. Parkinsonism Relat Disord 1998; 4(2): 59−60.
8. *Jankovic J.* Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008; 79(4): 368−76.
9. *Ebersbach G, Baas H, Csoti I, Müngersdorf M, Deuschl G.* Scales in Parkinson's disease. J Neurol 2006; 253 Suppl 4: IV32−5.
10. *Braak H, Del Tredici K.* Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology 2008; 70(20): 1916−25.
11. *Brooks DJ.* The early diagnosis of Parkinson's disease. Ann Neurol 1998; 44(3 Suppl 1): S10−8.
12. *Cookson MR.* alpha-Synuclein and neuronal cell death. Mol Neurodegener 2009; 4: 9.
13. *Gai WP, Blumbergs PC, Geffen LB, Blessing WW.* Age-related loss of dorsal vagal neurons in Parkinson's disease. Neurology 1992; 42(11): 2106−11.
14. *Jankovic J, Aguilar LG.* Current approaches to the treatment of Parkinson's disease. Neuropsychiatr Dis Treat 2008; 4(4): 743−57.
15. *Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW.* Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008; 14(5): 504−6.
16. *Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A,* et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 1997; 276(5321): 2045−7.
17. *Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M.* Alpha-synuclein in Lewy bodies. Nature 1997; 388(6645): 839−40.
18. *Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M.* alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci U S A 1998; 95(11): 6469−73.
19. *Uversky VN.* Intrinsically disordered proteins and their (disordered) proteomes in neurodegenerative disorders. Front Aging Neurosci 2015; 7: 18.
20. *Nelson R, Sawaya MR, Balbirnie M, Madsen AØ, Riekel C, Grothe R,* et al. Structure of the cross-beta spine of amyloid-like fibrils. Nature 2005; 435(7043): 773−8.
21. *Apetri MM, Maiti NC, Zagorski MG, Carey PR, Anderson VE.* Secondary structure of alpha-synuclein oligomers: characterization by raman and atomic force microscopy. J Mol Biol 2006; 355(1): 63−71.
22. *Pinotsi D, Buell AK, Galvagnion C, Dobson CM, Kaminski Schierle GS, Kaminski CF.* Direct observation of heterogeneous amyloid fibril growth kinetics via two-color super-resolution microscopy. Nano Lett 2014; 14(1): 339−45.
23. *Singh PK, Kotia V, Ghosh D, Mohite GM, Kumar A, Maji SK.* Curcumin modulates α-synuclein aggregation and toxicity. ACS Chem Neurosci 2013; 4(3): 393−407.
24. *El-Agnaf OM, Paleologou KE, Greer B, Abogrein AM, King JE, Salem SA,* et al. A strategy for designing inhibitors of alpha-synuclein aggregation and toxicity as a novel treatment for Parkinson's disease and related disorders. FASEB J 2004; 18(11): 1315−7.