EXPERT REVIEWS

XVIII WFN World Congress on Parkinson's Disease and Related Disorders Synopsis

Expert Rev. Neurother. 10(3), 377–380 (2010)

Karen Frei and Erik Wolters[1]

[1]*Author for correspondence*
Dept of Neurology, VUMC Amsterdam, The Netherlands
Tel: +31 204 442 833
Fax: +31 204 442 800
e.wolters@vumc.nl

XVIII WFN World Congress on Parkinson's Disease and Related Disorders

Miami Beach, FL, USA, 13–16 December 2009

Several interesting concepts regarding Parkinson's disease were recently presented at the XVIII World Congress on Parkinson's disease. The theory of α-synuclein acting as a prion, resulting in the spread of Parkinson's disease, was presented and related to the Braak hypothesis of neuropathology of Parkinson's disease. Nonmotor symptomatology of Parkinson's disease was presented and also related to the above. Research was emphasized at the meeting, and novel compounds thought to slow the progression of the disease were mentioned. Clinical research methodology designed to best prove an agent as disease modifying, and the merits of clinical research, were debated. Finally, treatment strategies for early Parkinson's disease, as well as continuous dopamine stimulation, were presented. This article briefly discusses these concepts presented at this important meeting of the World Congress on Parkinson's disease.

During the highly successful XVIII World Congress on Parkinson's Disease (PD), held in Miami, FL, USA, on 13–16 December, several new and exciting theories were presented and discussed. The keynote speaker, Stanley Prusiner (University of California, CA, USA; and later, Warren Olanow [Mount Sinai School of Medicine, NY, USA]) proposed the concept of PD as a prion-like disease. This is not as far-fetched as it sounds. One of the pathological hallmarks of PD is the presence of Lewy bodies, eosinophilic inclusion bodies found in cell bodies of neurons. α-synuclein is the major protein component in Lewy bodies. Overexpression of α-synuclein appears to overwhelm the ubiquitin protease system. The excess α-synuclein tends to misfold and, when misfolded, to aggregate and to induce dopamine cell death in culture with inclusion bodies. The misfolded conformation tends to be a β-pleated sheet. Misfolded α-synuclein is proposed to act as a prion, transmitting itself from a Lewy body-laden cell into a 'healthy' cell. Similar to prions, it is thought that the abnormal α-synuclein acts as a template for conversion of the native form of α-synuclein. This concept originates from the finding of Lewy bodies in grafted embryonic mesencephalic cells, identified on autopsy over 10 years after transplantation. It appears as if misfolded α-synuclein was released and then taken up by the transplanted healthy neurons. α-synuclein has been identified in the cerebrospinal fluid from both PD patients and controls, supposedly released through both exocytosis and cell death. The misfolded α-synuclein can be introduced into a 'healthy' cell through the process of endocytosis or passive membrane translocation. With excessive α-synuclein expression both monomers and aggregates are released. This prion-like transmission of misfolded protein molecules that tend to aggregate, overwhelm the ubiquitin protease system and result in cell death, may be a common mechanism for other neurdegenerative diseases, such as the tau protein in frontal temporal dementia and huntingtin in Huntington's disease.

This prion theory also ties in neuropathology of PD, according to the Braak hypothesis. Braak *et al.* proposed the staging of PD based upon the presence of Lewy bodies in the olfactory bulb, autonomic nervous system and lower brainstem regions early in PD, which later spread to involve the midbrain and finally the cortex. We look forward to future research to further delineate this concept and our evolving idea of PD.

 10.1586/ERN.10.18 ISSN 1473-7175

The nonmotor symptoms of PD was another important topic, discussed at the first plenary session of this meeting. These symptoms, as presented by Erik Wolters (VU University Medical Center, Amsterdam, the Netherlands), were correlated with neuropathology (Dennis W Dickson [Mayo Clinic Florida, FL, USA]) and neuroimaging (A Jon Stoessl [University of British Columbia & Vancouver Hospital, Canada]). Nonmotor symptoms, often occurring early in the disorder prior to the onset of motor symptoms, include autonomic nervous system dysfunction and olfactory bulb dysfunction. Autonomic nervous system dysfunction involves mainly the gastrointestinal system and cardiac system. Gastrointestinal symptoms are composed of upper GI tract symptoms, such as dysphagia, sialorrhea, abdominal discomfort, delayed gastric absorption and nausea, and lower GI tract symptoms of constipation. Cardiac sympathetic denervation is thought to be responsible for the reduced cardiac output, vasodilation and orthostatic hypotension that are seen in PD. Later on in the disease progression, the parasympathetic ganglia might also be involved. The pathology involves Lewy bodies present in the sympathetic ganglia, including the stellate ganglion, enteric neurons and the olfactory bulb. Lewy bodies have been identified in the esophageal and gastric plexus of Meissner and Auerbach, which correlates with upper GI tract symptoms. Lower GI tract symptoms of constipation appear to be related to the reduced vagal output and possibly increased sympathetic inhibition of the lower intestine. Hyposmia may also predate the onset of motor symptoms by many years, due to α-synuclein pathology in the olfactory bulb, anterior olfactory nucleus, perirhinal cortex and amygdala. Pathology here rather correlates with the presence of Lewy bodies and not with the degree of neuronal loss. As the pathology correlates with the Braak hypothesis, where the earliest Lewy bodies are found in the medulla and olfactory bulb, it has been proposed that the agent responsible for inducing PD (possibly by generating misfolded α-synuclein) might enter through the GI tract and possibly the olfactory bulb. Timing of the autonomic nervous system dysfunction and hyposmia, however, does not always predate motor symptoms and can become more of a problem later in PD.

Additional nonmotor symptoms of PD include sensory abnormalities, not only hyposmia but also visual changes, such as reduction in color and contrast vision and pain. PD patients tend to have a lower pain threshold, due to involvement of the locus ceruleus, with pain in the shoulder the most common complaint. Pain has more than one cause, however, and may also be related to motor PD symptoms, such as muscle rigidity or dystonia. Additional autonomic nervous system dysfunction seen in PD includes the urogenital system. The urinary bladder tends to have a storage rather than a voiding problem in PD, as the sympathetic nervous system relaxes the bladder and the parasympathetic system contracts the bladder. In PD, lumbosacral parasympathetic denervation of the detrusor muscle and sphincter underlie a detrusor sphincter dyssynergia. Striatal D1 activity inhibits the micturation reflex and, as the dopamine D1 receptor is inhibited in PD, voiding problems in these patients may be treated with D1 receptor stimulation. Reduced libido and testosterone deficiency are also nonmotor symptoms of PD.

Progression of the disease to involve the pons, according to the Braak hypothesis, may be responsible for the sleep disorders seen in PD. These sleep disorders include symptoms related to dopamine deficiency, such as restless legs syndrome, or sleep fragmentation resulting from akinesia or nocturia. In addition, rapid eye movement (REM) behavior disorder and excessive daytime somnolence are also observed in PD. Serotonergic, cholinergic and noradrenergic neurons are thought to be involved in REM behavior disorder. REM behavior disorder is also seen in other conditions, such as normal aging, multisystem atrophy and progressive supranuclear palsy. During REM behavior disorder, the normal paralyzed state is not seen and the patient tends to act out their dreams. They may fight with an unseen opponent, run out for a pass or leave a sinking ship. As one can imagine, this can be dangerous for the patient and/or the spouse. Patients with an isolated REM behavior disorder have an increased risk for developing PD. Corresponding α-synuclein pathology is seen in the pedunculopontine, lateral dorsal tegmental, locus ceruleus, dorsal raphe and periaqueductal gray regions.

Depression, anxiety, cognitive dysfunction and dementia are neuropsychiatric complications of PD. Depression appears to be due to serotonergic, noradrenergic and dopamine deficiency, and appears to be correlated with reduced serotonin binding on imaging. Finally, dementia and cognitive dysfunction tend to occur late in the disease and at this point there appears to be diffuse cortical Lewy bodies. Cognitive impairment and hallucinations appear to be related to age and not to the length of time of PD affliction. Mild cognitive impairment mainly consists of executive dysfunction, goal-directed behavior and visual spatial abnormalities. Functional imaging studies have shown a shift to declarative memory circuitry. As the cerebellum and not the caudate was activated, this might explain the difficulty with multitasking seen in PD. Not necessarily, in PD-related dementia there might be concurrent Alzheimer's pathology consisting of amyloid plaques and tau tangles, or concurrent vascular pathology, although amyloid depositions are mainly seen in diffuse Lewy body dementia (DLBD). In DLBD, dementia with visual hallucinations and REM behavior disorder with fluctuations in the level of consciousness are seen in the early motor phase. PD dementia in distinction occurs following the presence of motor parkinsonism for at least one year. The clinical features of DLBD tend to be related to the severity of Lewy body pathology. Imaging studies here show the primary visual cortex involvement, which is not seen in Alzheimer's disease. Psychosis, mostly with visual hallucinations, usually occurs in the setting of dementia in PD, although psychosis is also observed with sleep–wake cycle disturbances, daytime occurrence of REM sleep and dopaminergic medication. Thus, it appears that PD is a multisystem α-synucleinopathy with both CNS and peripheral nervous system involvement and, in the later stages, cortical involvement.

Another theme presented at the meeting was the quest for slowing down the progression of PD. Shengdi Chen (Shanghai Institute for Biological Sciences, Shanghai, China) discussed promising Chinese herbal medication, such as curcumin or turmeric, a spice found in Chinese and Indian food that has been found to attenuate the MPTP-induced neuronal loss in cell cultures. Turmeric helps to maintain mitochondrial function and is an apoptosis inhibitor through JNK1 inhibition, which inhibits

phosphorylation and attenuates the release of cytochrome-3 from the mitochondria. Salidroside, another chemical used in Chinese medicine, displaying antihypoxic, antioxidant and antiapoptotic properties, also protects the mitochondria and has been found to attenuate MPTP-induced dopaminergic neuron loss. It increases expression of GDNF, DAT, VMAT2 and BCL2 and it inhibits caspase 3. In addition, tripchlorolide rescues dopaminergic neurons from MPTP toxicity; it has anti-inflammatory and immunosuppressive properties, stimulates microglia and inhibits monoamine oxidase-dependent dopamine metabolism, the activation of glutamate as well as the release of neurotoxins. A combination of turmeric, salidroside and tripchlorolide was suggested to slow the progression of PD through different pathways.

The concept of multiple pathways leading to a final common pathway in neurodegenerative diseases may explain the failure of developing a single therapeutic agent to treat the disease. Therefore, stopping one of the pathways is insufficient to stop the disease progression. A multimodal therapeutic approach seems to be necessary. The PD-related mitochondria complex-1 defect as well as the defect protein clearance system appear to be good targets. As in many of the genetic forms of parkinsonism the mitochondria are affected (e.g., *LRRK2*, *PINK2*, *DJ1*, *Omi/HrA2* and *Parkin* mutations); there are ongoing studies looking at the effects of coenzyme Q and creatine on mitochondrial function in PD. As for the protein clearance system, the ubiquitin protease system tags misfolded protein with ubiquitin. It is transported into a proteasome where it is degraded. An alternative pathway involves the heat shock proteins and lysosomes where autophagy takes place. Several targets of potential therapeutic benefit include prevention of protein misfolding, promoting protein refolding, facilitating clearance of misfolded proteins and blocking prion conformation, for example, α-synuclein.

Karl Kieburtz (University of Rochester, NY, USA) discussed recent new clinical trial designs, such as the delayed-start and delayed-withdrawal designs, thought to be able to show disease modification. Both the Earlier Versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study and the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study utilized these designs. The ELLDOPA study looked at treatment of early PD with levodopa. In this study, following a two week washout, the patients treated with levodopa continued to perform better than the patients given placebo. The ADAGIO study compared the placebo-controlled early versus later treatment of *de novo* PD patients with rasagiline 1 and 2 mg. Once again the 1-mg dose appeared to have both symptomatic as well as disease-modifying effects. However, the 2-mg-treated group showed only symptomatic effects. The results from both the ELLDOPA and ADAGIO studies continue to be debated. Additional clinical trial designs include the nonsuperiority and long-term disability trials. The Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD) studies utilized the nonsuperiority approach to identify potential therapeutic agents and the creatine study, still ongoing, is looking at long-term disability. Additional studies looking at the nonmotor symptoms need to be developed. A combination approach may be the best way to develop novel therapeutic agents starting with a nonsuperiority study, followed by a delayed-start design study and completed with a long-term disability study. Russell Katz from the US FDA also discussed the various clinical trial designs thought to show disease-modifying properties. While the delayed-start or delayed-withdrawal designs may be closest to being able to prove disease modification, there are debatable aspects of both. Further discussion of the value of randomized clinical trials by William Weiner (University of Maryland, MD, USA) reminded us of the value of natural history studies, anecdote, trial and error and experience to the treatment of the PD patient.

Treatment of early PD, discussed by Robert Hauser (University of South Florida, FL, USA), includes the use of a monoamine oxidase-B inhibitor, dopamine agonists and/or levodopa. It appears that early treatment is desirable in an attempt to slow disease progression. Both rasagiline and selegiline show modest symptom alleviation, but may improve long-term outcome. Selegiline in addition to levodopa was found to give better results in the long term than treatment with levodopa alone. Dopamine agonists can delay the need for levodopa but tend to have a greater amount of side effects, including impulse control disorders and excessive daytime somnolence. Levodopa can be useful to treat early PD especially in those intolerant of dopamine agonists.

Additional treatment strategies, including continuous dopamine stimulation, were also discussed. In the normal state, dopamine receptors are continuously stimulated. In PD-related dopamine deficiency, treatment with the oral dopamine precursor levodopa, with a typical short half-life, is thought to produce dyskinesias and motor fluctuations. Continuous treatment with the apomorphine subcutaneous pump and the levodopa-carbidopa intestinal gel pump were discussed. These strategies tend to provide a more continuous drug delivery, and may thus more closely approximate the normal state. Treatment with the duodenal levodopa-gel in particular seems highly successful, not only in bringing down the dyskinesias but also by further improving motor and non-motor signs and symptoms. Currently available alternative non-invasive methods to reach more continuous dopamine receptor stimulation include the use of catechol-*O*-methyl transferase inhibitors, such as entacapone or tolcapone. However, the Stalevo Reduction in Dyskinesia Evaluation (STRIDE) PD study did not show early use of Stalevo® (Comtan® plus carbidopa-levodopa) to be beneficial in the prevention of dyskinesias. Future development of long-acting levodopa preparations, such as the ethyl ester of levodopa delivered through a transdermal patch, may provide the continuous dopamine stimulation required to prevent dyskinesias and motor fluctuations and thus provide superior symptomatic treatment.

Tetrabenazine was discussed as an effective treatment for hyperkinetic disorders, such as Huntington's disease, Tourette's syndrome and tardive dyskinesia. There was also great interest in the use of sonography for the diagnosis of PD and the use of botulinum toxin for drooling.

As more research evolves, new treatments and therapeutics will be able to be presented at the next WFN World Congress on Parkinson's Disease and Related Disorders where the theme will be Old Meets New, held in Shanghai, China in 2011.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Affiliations

- Karen Frei, MD
  The Parkinson's and Movement Disorders Institute, Fountain Valley, CA, USA
- Erik Wolters, MD, PhD
  Dept of Neurology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
  Tel: +31 204 442 833
  Fax: +31 204 442 800
  e.wolters@vumc.nl