

## **Meeting Report: XX WFN World Congress on Parkinson's Disease and Related Disorders**

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### *Abstract:*

*The twentieth World Congress on Parkinson's Disease and Related Disorders was held December 8<sup>th</sup> through 11<sup>th</sup> at the city of Geneva. Geneva is home to the Red Cross and the United Nations, a fitting site for this international meeting to take place. This meeting sponsored by the International Association of Parkinsonism and Related Disorders presented updates in the field of movement disorders with an emphasis on motor behavioral and behavioral motor disorders. Research was presented at the meeting and novel compounds and treatments were mentioned. Synopses of the presentations on behavior in Parkinson's Disease, physiology of tremor and Deep Brain Stimulation therapy are included.*

The twentieth World Congress on Parkinson's and Related Disorders was held December 8<sup>th</sup> through 11<sup>th</sup> at the city of Geneva. Geneva is home to the Red Cross and the United Nations, a fitting site for this international meeting. Emphasis was on behavioral movement disorders including the physiology of behavior in Parkinson's disease (PD), dopamine and behavior and the phenotype of synucleinopathies. These topics along with the physiology of tremor and updates in Deep Brain Stimulation (DBS) therapy are briefly discussed.

The physiology of behavior was presented by Mark Hallett (USA). The posterior part of the brain is the sensory portion receiving visual, somatosensory and auditory information from the environment. This information is then integrated in

multisensory regions in the parietal lobe and is the source of external triggering of movement. The front part of the brain receives and integrates information about the body and is considered the source of internal triggering e.g. hunger and thirst from the hypothalamus. Other internal triggers come from the limbic system consisting of vigilance, fear, anxiety and sex and from the mesolimbic dopaminergic system consisting of reward. Internal and external inputs are integrated in the mesial frontal areas such as the cingulate, presupplementary motor and premotor areas. Environmental stimulation and multiple forces from internal drives influence behavior.

Behavioral abnormalities due to reduced internal triggers include akinesia, hypokinesia and bradykinesia. The basal ganglia support the part of the brain where internal triggering of movement is generated. Basal ganglia dysfunction results in difficulty generating and initiating movement producing slow and small movements. Greater attention to movement helps to compensate. Externally triggered movements require less basal ganglia support underlying the phenomenon of paradoxical kinesia. Sequence effect is when repetitive movements become gradually slower or smaller. This is seen in PD with handwriting, commonly precedes freezing of gait and is not responsive to dopamine. It may be unique to PD.

Six examples of disorders of volition include: tics in which voluntary movements occur, but the patient's allow the movements to happen and do not make the movements; psychogenic movements which involve normal appearing movements that are believed to be involuntary; Huntington's chorea where early on in the disease patients believe their movements to be voluntary; anosognosia in which the patient believes they have moved when they have not; alien hand where unwanted movements occur without the sense that they are willed movements and

schizophrenia in which the movements appear to be normal, however, the patient may believe they are being controlled.

John Caviness (USA) spoke on pathophysiology of Parkinsonian behavior; starting with molecular pathology which leads to neurochemical changes leading to site and circuit dysfunction resulting in global network activity and producing abnormal behavior. With respect to PD, it is not known how misfolded alpha synuclein leads to neuronal death. The site of dysfunction is the substantia nigra with the circuit affected the frontostriate circuit. Striatal dopamine depletion alters the basal ganglia output to the frontal cortex through the thalamus. Frontal cortical areas commonly contain Lewy bodies and frontal/executive cognitive deficits are common in PD. Executive dysfunction, mood alterations, apathy and poor motivation are behavioral manifestations related to frontal lobe dysfunction in PD.

A theory related to behavior in PD was presented by Peter Redgrave (United Kingdom). There are two behavioral control systems: goal directed control (GDC) and habitual control (HC). In GDC, behavioral selections are determined by relative outcome values of competing actions. With HC behavioral selections are based upon previously learned stimulus- response associations. GDC behaviors appear to be driven by associative loops located in the anterior dorsomedial striatum. HC behaviors are driven by sensorimotor loops located in the posterior putamen. In PD there is preferential dopamine loss in the sensorimotor territories associated with HC behaviors. With the loss of HC behaviors there is reliance upon GDC behaviors which are slower, involve more effort and are volitional. Therefore walking becomes a task requiring much attention and patients cannot execute simultaneous or sequential motor programs.

The role of dopamine in behavior and PD was discussed by Antonio Strafella (Canada). Dopamine is involved with three main pathways: the nigrostriatal, the mesolimbic and mesocortical pathway. The nigrostriatal pathway is involved in motor planning and execution. The mesolimbic and mesocortical dopaminergic pathways are involved in cognitive, emotional processes and regulation of reward related learning mechanisms. Dopamine appears to influence the selection of an optimal response from competing motor or cognitive programs by facilitating the relevant program while inhibiting irrelevant ones. A reduction in dopamine results in depression and apathy while an increase results in impulse control disorders, compulsive medication use and punning. In addition, dopamine depletion may set up development of impulse control disorders by producing sensitization of post synaptic neurons altering the mesocorticolimbic circuit.

Synucleinopathies comprise a group of neurodegenerative disorders characterized by abnormal accumulation of the protein synuclein. The different phenotypes of synucleinopathies were presented by Glenda Halliday (Australia). There are three genes which produce synuclein and several isoforms of synuclein which can easily change conformation. Abnormal accumulation of alpha-synuclein insoluble aggregates found in neuronal or glial cells characterizes alpha-synucleinopathy. Primary alpha-synucleinopathies include PD, DLBD and multisystem atrophy (MSA). Secondary forms comprise Alzheimer's disease and neuroaxonal dystrophy. A rare mutation in beta -synuclein has been found in Diffuse Lewy Body Dementia (DLBD). There is no accumulation of beta-synuclein, but those with pure DLBD have reduced beta-synuclein in the cortex. Mutations in gamma-synuclein cause breast cancer. Alpha synuclein has the ability to self-aggregate and is the major protein found in Lewy body inclusions, glial cytoplasmic inclusions and axonal spheroids. Lewy bodies are composed of alpha-synuclein, not beta-synuclein.

Alpha-synuclein gene mutations and multiplication of the alpha-synuclein gene result in PD. Polymorphic variability in the alpha-synuclein gene creates risk for development of PD.

Beta-synuclein lacks aggregation properties, but can form oligomers. The Beta-synuclein oligomers can bind to oligomeric alpha-synuclein and this complex becomes insoluble but is stable and does not propagate. Normal functioning beta-synuclein inhibits the aggregation of alpha-synuclein and formation of alpha/beta oligomeric complex. Pathologically, DLBD have substantial cortical amyloid deposition, Lewy bodies present in the amygdala, frontotemporal atrophy with white matter involvement and hippocampal neuronal cell loss. DLBD has deposition of alpha-synuclein and alpha and beta oligomeric complexes with a greater amount of alpha-synuclein deposition compared to PD. DLBD has a faster rate and greater spread of neurodegeneration than PD. It is thought that reduced beta-synuclein function contributes to these differences.

Alpha-synuclein aggregates are found in oligodendrocytes in MSA. Oligodendrocytes do not produce alpha-synuclein normally. There is substantially increased amount of alpha-synuclein in MSA compared to PD. MSA has a faster rate of progression and greater spread of neurodegeneration compared to PD. Reduced growth factor function is thought to be implicated in these differences.

The pathophysiology of tremor was presented by Mark Hallett (USA). The basal ganglia network is linked to the cerebello-thalamo-cortical network. A theory behind the parkinsonian tremor includes dysfunction in the basal ganglia triggering tremor driving the cerebello-thalamo-cortical network. In essence the basal ganglia act as the light switch turning on the tremor and the cerebello-thalamo-cortical network acts as the dimmer controlling the amplitude of the tremor. However, the specific

generator node in the basal ganglia has not been identified. The network oscillates at rest and in stable posture and motor commands coming through the network disrupts the tremor oscillations.

Essential tremor (ET) occurs in posture or with movement and is generated by the cerebello-thalamo-cortical circuit. Initiation of the tremor may involve a cerebellar abnormality of GABA, possibly involvement of the inferior olive or spontaneous activity in the VIM thalamic cells. Studies have been controversial. Both PD and ET share the cerebello-thalamo-cortical network as the generator of the tremor. However in ET it appears as though the motor controller of the cerebellum is dysfunctional setting off oscillations triggered by movement.

Beta oscillations and closed loop DBS were discussed by Peter Brown (United Kingdom) and Andres Lozano (Canada). Beta oscillations, the  $\sim 20$  Hz waveforms found on EEG, are ubiquitous throughout the cortical-basal ganglia circuitry in PD. Increased beta oscillations are associated with slowing of spontaneous movement and corrective responses to postural perturbation. Overall beta levels are correlated with rigidity and bradykinesia at rest. Beta activity is likely controlled by the level of dopaminergic activity in response to internal and external cues and serves to modulate the stability of the current motor state. Closed loop DBS with high frequency stimulation given only when beta activity is high appears to be effective, with control of PD symptoms including tremor and uses less energy, thereby extending battery life.

Alternative DBS sites include the pedunculopontine nucleus to improve gait and the Nucleus Basalis of Meynert to improve memory. Future developments in the field of DBS include new electrode designs for spatial current steering, more physiological

patterns of stimulation, improvement in imaging modalities to better visualize the brain target and better MRI compatibility with DBS hardware.

This was just a few of the highlights from the XX World Congress on Parkinsonism and Related disorders. See you in Milan in 2015.

## References

Parkinson Disease and Other Movement Disorders: Motor Behavioural disorders and Behavioural Motor Disorders. Wolters E and Baumann C (Eds.), VU University Press, Amsterdam, The Netherlands (2014).

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