Neuroprotection in Parkinson's Disease

International Consensus Conference

The Pontifical Academy of Sciences, whose purpose is to promote the progress of the sciences for the common good of the human person, in its Study Week of 5-6 April 2011 at its headquarters in the Vatican, would like to focus on the wellbeing of the nervous central system, taking into account the revolutionary contributions of the last century in relation to the human brain and movement. PD is a neurodegenerative disorder characterized by degeneration of dopamine neurons in the substantia nigra pars compacta (SNc) coupled with intracellular proteinaceous inclusions or Lewy bodies. Current therapies effectively treat dopaminergic motor features. However, features emerge that are not satisfactorily controlled with dopaminergic therapies, such as falling, freeing, and dementia that are not adequately controlled with available medical or surgical therapies. Indeed, these “non-dopaminergic” features represent the major source of disability and need for nursing home placement in advanced PD patients. A disease-modifying or neuroprotective therapy that slows or stops disease progression and prevents the emergence of these problems is an urgent priority. Both autosomal-dominant and recessive gene mutations have been reported to cause PD. There is also evidence that environmental factors contribute to the etiology of PD, as suggested by the association of parkinsonian syndromes with exposure to neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or hydrocarbons. Further, epidemiological studies indicate that rural living, well-water consumption and exposure to pesticides increase the risk of developing PD, whereas there is a decreased risk of PD associated with smoking and coffee consumption. None of these factors, however, explain the large majority of cases that appear to have a sporadic form of the disease. Indeed, twin studies suggest that genetic factors probably play a dominant role in young-onset cases where environmental factors are likely to be more

important in most older sporadic cases. It is likely that sporadic PD is related to a complex interaction between a variety of genetic and environmental factors that may be different in different individuals. This implies that there are many different causes of PD and makes it unlikely that a single neuroprotective treatment aimed at interfering with a single etiologic factor will be effective in the majority of PD patients. Other opportunities for neuroprotection in PD derive from studies on the pathogenesis and mechanism of cell death.

Current information suggests that neurodegeneration in PD is associated with a cascade of events including oxidant stress, mitochondrial abnormalities, excitotoxicity and inflammation. Based on this evidence, a number of theoretical neuroprotective strategies can be designed. What is not clear, however, is whether these processes are primary or secondary, which if any is the driving force that initiates neurodegeneration and what role each plays in the neurodegenerative process that occurs in an individual patient. While no therapy has as yet been demonstrated to be neuroprotective in PD, it is anticipated that with advances in mechanisms responsible for cell death, better animal models in which to test promising new therapies, and new clinical trial designs such as delayed-start and long-term simple study, disease-modifying drugs will soon be forthcoming. Indeed, we and others have recently demonstrated in a large delayed start study that early treatment with rasagiline 1 mg provides benefits that are not achieved with delayed introduction of the same therapy, consistent with a disease-modifying effect. The development of a marker of pre-motor PD would offer many important advantages. First, it would help to define an at-risk population that could be used in clinical trials to help develop a disease-modifying therapy. If it could be determined that a therapy has a disease modifying effect, introduction of such an agent at the earliest possible time point might be essential in order to maximize its effect on disease progression. Indeed, introduction of an effective disease-modifying agent in the pre-motor stage might significantly delay or even entirely prevent the development of the classical motor features of the disease. Pathology studies indicate that neurodegeneration with Lewy body and Lewy neurite pathology affects multiple non-dopaminergic sites throughout the central nervous system and the peripheral autonomic nervous system. This non-dopaminergic pathology is thought to account for the non-dopaminergic features of PD. Further, Braak and colleagues have suggested that alpha synuclein pathology accumulates in a sequential manner, with degeneration of SNc dopamine neurons occurring at a mid-stage of the disease. In keeping with these pathologic findings, numerous studies indicate that several non-dopaminergic clinical features precede, or represent risk factors for, the development of the classic motor features of PD. These include anosmia, constipation, depression and REM behavior sleep disorder (RBD). Indeed, studies suggest that these non-motor features can predate the development of motor features by several years. Further, anosmia and RBD are associated with reduced striatal uptake of biomarkers of nigrostriatal function and anosmia, and reduced FD uptake on PET in first degree family members of PD patients are associated with a strikingly greater risk that the patients will be diagnosed as having PD. Recently a large number of studies are trying to find these kinds of precocious symptoms, in order to obtain an early diagnosis, possibly in a pre-clinical (or pre-motor) phase, and test drugs capable of slowing down or stopping degeneration. Often several symptoms like anosmia, some sleep disorders and constipation appear before motor symptoms.

Hypo/anosmia is a characteristic premotor symptom in PD complex; in a recent review, Haehner found the prevalence of smell disorders should be more than 95% and should be present also in the early stage of the disease. Ponsen and coll. found a high risk of developing PD in first degree PD relatives. Several lines of evidence suggest that dopamine denervation of the heart might also precede the onset of PD motor features. This international symposium on neuroprotection in PD will be focused on discussion about all these topics, bringing together the top experts in the field. The meeting will be a great occasion to reach a consensus on debated topics and design a common research line to achieve neuroprotection in PD. The proceedings of the meeting, including the discussion will be published in the prestigious journal *Movement Disorders*.

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