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Preface – Special issue: Multiple system atrophy

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In 1969, Graham and Oppenheimer introduced the term multiple system atrophy (MSA) to denote a neurodegenerative disease characterized clinically by varying combinations of autonomic, parkinsonian, cerebellar or pyramidal symptoms or signs, and neuropathologically by cell loss and gliosis in the basal ganglia and olivopontocerebellar system. They deserve recognition for having identified as a single entity a disease that previously had been reported under the rubrics of olivopontocerebellar atrophy, idiopathic orthostatic hypotension, Shy-Drager syndrome and striatonigral degeneration depending upon the clinical presentation.

This special issue of *Journal of Neural Transmission* contains the invited lectures presented as part of the Second International Meeting on MSA in Rome on June 17–18, 2004. This meeting followed a previous one dedicated to this challenging neurodegenerative disease that had been held in London in 1997.

Since the meeting of investigators concerned with MSA in 1997, several new advances in our understanding of the cellular pathology and clinical features of MSA have been reported. In the late nineties α-synuclein was recognized as a major component of glial cytoplasmic inclusions (GCIs), which represent the specific inclusion pathology found in the brain of patients with MSA regardless of clinical presentation (Spillantini et al., 1998). Based upon these developments in molecular pathogenesis, MSA has been firmly established as α-synucleinopathy along with Parkinson's disease and dementia with Lewy bodies.

In parallel with improved understanding of molecular pathogenesis, recognition of MSA as a clinical entity greatly improved following the introduction of new diagnostic criteria. Quinn first proposed in 1989 a list of diagnostic criteria (Quinn, 1989). He divided MSA patients into two major categories: those presenting with predominantly parkinsonian signs ("MSA-SND") and those with predominant cerebellar involvement ("MSA-OPCA"). Within each of these groups patients were labelled as clinically possible or probable according to the extent to which multiple systems were involved. Cases were classified as definite only when neuropathological confirmation was obtained. These

purely clinical criteria were revised in 1994 to include evidence of abnormal sphincter EMG (Quinn, 1994). In the late nineties a number of pitfalls associated with the Quinn criteria were identified. These were: (1) the need for rigorous criteria for orthostatic hypotension; (2) the importance of urinary incontinence for diagnosis; (3) abnormal sphincter EMG had been reported in other disorders, hence it was not specific for MSA; and (4) redundancy in the classification.

New diagnostic criteria were therefore developed by a consensus conference based on four clinical domains, including autonomic and urinary dysfunction (which has now a central role in classifying a patient as probable MSA), parkinsonism, cerebellar dysfunction and corticospinal tract dysfunction (Gilman et al., 1999). The two motor presentations of MSA (parkinsonism and cerebellar ataxia) were designated MSA-P and MSA-C, replacing the previous terms MSA-SND and MSA-OPCA. The consensus criteria have since been widely established in the research community as well as movement disorders clinics. A retrospective evaluation of the consensus criteria showed excellent positive predictive values for both possible and probable MSA. However, sensitivity for probable MSA was suboptimal (Osaki et al., 2002). Whether the consensus criteria will improve recognition of MSA patients, especially in early disease stages, needs to be investigated by prospective surveys with pathological confirmation in as many cases as possible. As magnetic resonance imaging (MRI) studies have demonstrated findings relatively specific to MSA, the consensus criteria should be updated to include MRI, and possibly other imaging modalities such as positron emission tomography. Plans are currently being developed to convene a further consensus meeting in the near future.

Although therapeutic options are limited at present, there is hope for development of treatments for this devastating illness. Two European (EMSA-SG, NNIPPS) and one North-American (NAMSA-SG) research initiatives are presently functioning, and in two cases already conducting, multicentre intervention trials in MSA. These trials hopefully will change our approach to MSA. Furthermore, prospective clinical and laboratory data concerning disease progression will become available, allowing us to reliably identify variables that predict survival. Surrogate markers of the disease process will be identified, allowing the planning of future phase III intervention trials more effectively. To this regard, a specific rating instrument (Unified MSA Rating Scale, UMSARS), including a video teaching tape, has been developed by the EMSA-SG (Wenning et al., 2004) to standardize severity assessments in specialized clinics and research programs worldwide.

A number of animal models (using local and systemic neurotoxins) have become available as test beds for preclinical intervention studies (Scherfler et al., 2000; Ghorayeb et al., 2000). Recent transgenic mouse models overexpressing human wild-type α-synuclein in oligodendrocytes also mimic the molecular pathology of MSA, including the accumulation of GCIs in the glia (Kahle et al., 2002; Stefanova et al., 2005; Yazawa et al., 2005). Work along these lines will lead to a better comprehension of the pathopysiology of this disorders and, hopefully, to a number of candidate neuroprotective agents ready for evaluation during the next decade.

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