A milestone on the way to therapy for MSA

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterised by parkinsonian, cerebellar, autonomic, and pyramidal symptoms; autonomic failure and either parkinsonism or cerebellar ataxia confirm a clinical diagnosis. Pathological changes in MSA include cell loss, gliosis, and α-synuclein-positive glial cytoplasmic inclusions in the brain and spinal cord. However, an effective treatment that can modify the disease progression has not yet been established.

In this issue of The Lancet Neurology, Gregor Wenning and colleagues from the European MSA Study Group report a multicentre-based prospective cohort study of 141 patients with MSA to identify predictive clinical factors for survival and deterioration of activities of daily living. They found that the parkinsonian variant of MSA and incomplete bladder emptying were significant predictors of survival. They also showed that a shorter disease duration at baseline and an absent levodopa response predicted rapid progression on the unified MSA rating scale (UMSARS), which was designed and validated by the European MSA study group as a quantitative outcome measure. Additionally, many aspects of the disease are well described, particularly a sample size estimation for an interventional clinical trial with 1-year follow-up by UMSARS. This study confirmed and extended previous findings about the natural history of MSA and, importantly, provides useful information not only for patient counselling, but also for planning of multicentre trials for novel drug development.

In MSA, several compounds have shown positive results in animal studies, cell culture studies, and exploratory clinical studies, but there has been no drug with confirmed efficacy in large clinical trials. Developing a disease-modifying therapy for MSA has been hampered by several problems: limited natural history data; insufficient knowledge about the mechanisms of neuronal and glial cell loss; the scarcity of animal models that reflect human pathology; and the absence of tests to diagnose presymptomatic individuals or patients at very early stage of disease. However, by addressing the issue of natural history, Wenning and colleagues have opened new scientific frontiers for developing more reliable clinical trial designs, and, thereby, the possibility of new treatment for MSA.

Unlike for symptomatic relief treatments, such as levodopa for Parkinson’s disease and cholinesterase inhibitors for Alzheimer’s disease, a clinical trial design for disease-modifying therapies that slow or prevent neurodegeneration has not yet been established. Successful translational research of neurodegenerative diseases requires the identification of a target molecule that is closely involved in the pathogenesis of neurodegeneration. However, a more important aim is to establish a detailed prospective natural history with quantitative outcome measures, to define sensitive and validated disease-specific endpoints needed for effective clinical trials. On the basis of recent studies such as active immunisation with an amyloid β vaccine for Alzheimer’s disease and ligand-targeted therapies for spinal and bulbar muscular atrophy, the duration of disease seems to be a crucial factor, with unequivocal effect on the outcome of the trial. The effects of disease-modifying therapies might be limited at even early symptomatic stages, because neuropathological changes progress during the presymptomatic stages. Furthermore, to develop novel neuroprotective therapies, study of earlier MSA cases, including patients with presymptomatic or premotor MSA, and identification of biomarkers to diagnose the disease at these stages, will increase the chances of success of future clinical trials.

In the medical care of patients with MSA, we need to establish the optimum time to introduce non-invasive positive pressure ventilation, tube feeding, and tracheostomy. Thus, the ability to predict several clinical milestones, such as those studied by Wenning and colleagues (gastrostomy, unintelligible speech, daily falls, inability to walk, and death), is valuable. There are some limitations in this study, such as a short follow-up period (2 years for UMSARS assessments), a low follow-up ratio (43 patients with total UMASRS data available at 24 months), and a small number of cases, which reduce the number of patients who reached each milestone. The causes of death were also not established. Longer-term follow-up periods and a higher follow-up ratio are needed to identify the overall progression and prognosis of MSA.

Although solving all the problems inherent in treating MSA is difficult, this study by the European MSA Study Group has greatly contributed to the
establishment of many clinical features of MSA, and has shown the importance of a large multicentre study for documenting the prospective natural history of this rare type of neurodegenerative disorder. UMSARS will also play an important part as a clinical outcome measure in promoting future clinical trials of MSA. Further international co-operative studies will clarify the overall natural history, and enable potential therapeutic interventions to be initiated at an early stage.

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We declare that we have no conflicts of interest.