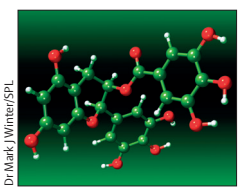
Neuroprotection in multiple system atrophy: unresolved issues



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See Articles page 724

Multiple system atrophy is a neurodegenerative disease that affects 1·9–4·9 people per 100 000 population; it is one of the main differential diagnoses of Parkinson's disease in a patient with neurodegenerative parkinsonism.[1] People with multiple system atrophy quickly develop severe disabilities, including autonomic dysfunction—eg, severe orthostatic hypotension, urinary incontinence, difficulty breathing and sleeping—dysarthria, dysphagia, and problems with gait and balance. The disease is sporadic and its cause is mostly unknown.[1] Pathology is characterised by widespread glial cytoplasmic inclusions composed of aggregated α-synuclein—ie, the same protein involved in the pathogenesis of Parkinson's disease and in degeneration of the nigrostriatal and olivopontocerebellar structures. Definite diagnosis is possible only post mortem; diagnosis in vivo is based on clinical criteria. There is no biomarker for multiple system atrophy, and no efficacious symptomatic or neuroprotective therapies are available.[1] Thus, as for other neurodegenerative proteinopathies, finding a treatment for multiple system atrophy is imperative.

In *The Lancet Neurology*, Johannes Levin and colleagues[2] report the results of a 52-week, randomised, double-blind, placebo-controlled trial investigating whether the polyphenol epigallocatechin gallate, an α-synuclein aggregation inhibitor, is safe and efficacious in slowing disease progression in 92 patients with possible or probable multiple system atrophy. The primary endpoint was the change from baseline to week 52 in the motor examination score of the Unified Multiple System Atrophy Rating Scale (UMSARS). The mean change from baseline in motor examination scores of UMSARS at week 52 did not differ significantly between the epigallocatechin gallate and placebo groups (5·66 [SE 1·01] *vs* 6·60 [0·99]; mean difference −0·94 [SE 1·41; 95% CI −3·71 to 1·83]; p=0·51). Epigallocatechin gallate was well tolerated but was associated with hepatotoxicity in some patients. Brain atrophy changes were assessed at week 52 as secondary imaging outcomes in an MRI sub-study of 32 patients. These imaging analyses suggested reduced brain atrophy in the 11 patients in the epigallocatechin gallate group compared with the eight patients in the placebo group who completed the MRI sub-study.[2]

Levin and colleagues' study is one of the largest and best-designed clinical trials that has been done in patients with multiple system atrophy, but joins the list of clinical trials with negative results from the past decade. Their study also addressed some of the main criticisms of previous double-blind trials with negative results in patients with multiple system atrophy. They chose a highly relevant therapeutic target (α-synuclein aggregation) on the basis of a strong rationale from preclinical studies, administered the highest tolerated dose, applied available clinical natural history data, used evidence-based data for power calculations and identification of the minimally clinically important change in the primary outcome, and used an imaging surrogate marker (ie, brain atrophy).[3,4] Perhaps the definition of a treatment effect as a 50% reduction in UMSARS motor examination scores was too ambitious, but the positive finding of reduced brain atrophy in the MRI sub-study, even if the number of patients was low, is the first positive result in a double-blind trial in patients with multiple system atrophy, and warrants further research. Furthermore, despite the unsatisfactory findings for the primary outcome, this study adds to the knowledge gained from other clinical trials, helps to advance the field, and could potentially drive improved design of future studies with better chances of success.

A major issue in multiple system atrophy is the validity of preclinical data. Epigallocatechin gallate almost completely blocks pathological α-synuclein aggregation in in-vitro cellular and cell-free experiments, and thus there is a clear gap between preclinical models and the natural disease course in human beings. Therefore, improvement of preclinical models is crucial. Characterisation of transgenic models of multiple system atrophy by using non-motor endpoints, wet biomarkers, and multimodal neuroimaging; understanding the genetics and underlying pathogenesis; and the generation of hypothesis-blind disease models (ie, induced pluripotent stem cells) are considered top research priorities that are important for the design of better clinical trials in future.[5] Identification of imaging (such as α-synuclein PET) and non-imaging biomarkers

by establishing large international biomarker cohorts is another priority.[5] Accuracy of early clinical diagnosis is still an issue, with a high frequency of misdiagnosis particularly in the early stages of disease. Clinical criteria that were last revised more than 10 years ago are still in use. The need to revise these criteria to enable accurate diagnosis early in the disease course has been identified, and a revision is planned.[6]

Levin and colleagues' study showed that these unresolved issues could be crucial hurdles on the way to identification of a neuroprotective treatment for multiple system atrophy. Despite the positive aspects and gains of their trial, an efficacious treatment for patients with this devastating disease is still not available.

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I declare no competing interests.

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Restoring function in progressive multiple sclerosis

The use of frames and tilt tables to support passive standing for people with lower limb paralysis has been part of the entry-level training of physiotherapists for more than 60 years. In 1955, Marjorie Farnbach[1] described such practice of passive standing in patients with poliomyelitis, stating that "the length of time spent in this standing frame varies from a few minutes at first with increasing periods as they can be tolerated up to several hours daily." In a paper[2] published in the preceding year, Willhite and colleagues outlined the development of an apparatus used to place the patient "in the standing position for weight-bearing purposes", to "prevent demineralisation" of bone and obtain "better postural control alignment". But, despite the many reports of the advantages of supported standing, research examining this approach in people with chronic neurological conditions has been inconclusive, with some studies suggesting that the intervention provided no meaningful benefits to mobility or lower extremity range of motion.[3-6]

In *The Lancet Neurology*, the Standing Up in People with Progressive Multiple Sclerosis (SUMS) study done by Jennifer Freeman and colleagues,[7] with a randomised controlled trial design, provides the first high-quality evidence that using a standing frame for 20 weeks at home can reduce lower extremity contracture and enhance mobility in people with disability related to severe multiple sclerosis.[8] In the trial, participants had two home-based physiotherapy sessions to set up the standing frame and six follow-up telephone calls. Participants were asked to stand for 30 min, three times per week over 20 weeks, and encouraged to continue in the longer term, but without further physiotherapy support provided. Participants who used the standing frame (n=71) had a significant increase in Amended Motor Club Assessment (AMCA) score compared with that in participants who had usual care alone (n=69), with a fully adjusted between-group difference in AMCA score at 36 weeks of 4·7 points (95% CI 1·9–7·5; p=0·001). The frequency of short-term musculoskeletal pain was higher in the standing frame group than in the usual care group (486 [41%] of 1188 adverse events *vs* 160 [22%] of 736 adverse events), which was potentially related to the intervention.

This positive outcome begs the question: "how does the intervention provided in Freeman and colleagues' study differ from other supported standing programmes described in previous research"? The following are probably some of the features that made a difference in the supported standing intervention provided in the SUMS trial.


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See **Articles** page 736