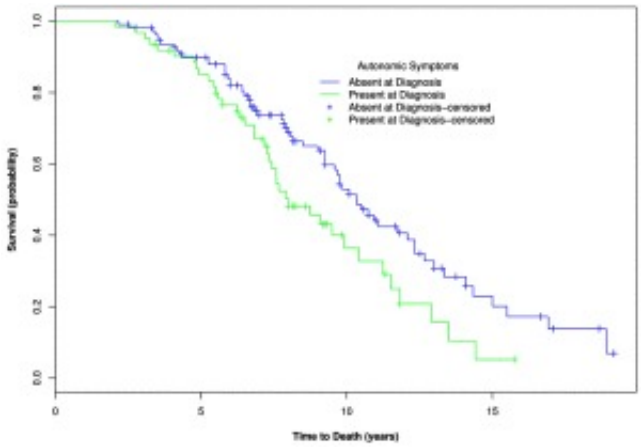
Natural history of multiple system atrophy in USA

Multiple system atrophy (MSA) is a rare, fatal brain disorder exhibiting a combination of parkinsonism and/or cerebellar gait unsteadiness and autonomic failure. Autonomic failure, manifest as orthostatic hypotension, severe constipation and urinary incontinence or retention, as well as sleep and breathing problems are typical as the disease progresses. Retrospective studies have provided important information on its clinical features and prognosis, but there has never been a prospective study on patients in the United States. We report the first US prospective natural history study of MSA, to compare the parkinsonian variety (MSA-P) and cerebellar variety (MSA-C) and to determine what features predict outcome.



Kaplan-Meier survival curves for probability of dying in subjects with severe symptomatic autonomic failure at diagnosis compared with those without severe symptomatic autonomic failure at diagnosis.

We evaluated 175 patients with probable MSA, both MSA-P and MSA-C. These patients were recruited and prospectively followed for 5 years with evaluations every 6 months in 12 centers in USA. Natural history was evaluated by Kaplan-Meier survival analysis. We compared MSA-P with MSA-C and evaluated predictors of outcome. These subjects were evaluated with UMSARS I (a functional score of symptoms and ability to undertake activities of daily living), UMSARS II (neurological motor evaluation), the Composite Autonomic Symptoms Scale (COMPASS)-select (a measure of autonomic symptoms and autonomic functional status), and COMPASS-select-change (a derivative of COMPASS-select where participants score how much their autonomic symptoms have changed).

We made the following main findings: Mean age of symptom onset was 63.4 (SD 8·57) years. Median survival from symptom onset by Kaplan-Meier analysis was 9.8 years. Patients with severe symptomatic autonomic failure at diagnosis had a worse prognosis, surviving a median of only 8.0

years while remaining subjects survived a median of 10.3 years (Figure). At baseline, MSA-P and MSA-C were not different in symptoms and function, or by examination. Median time to death from enrollment baseline was 1.8 years, indicating that patients had their disorder undiagnosed for most of its duration.

Take home messages: The use of strict Consensus criteria to diagnose probable MSA has resulted in improved certitude of diagnosis but delays diagnosis until a late-stage of the disease with short survival. The natural history of MSA-P and MSA-C are similar. Severe symptomatic autonomic failure at diagnosis (orthostatic hypotension or urinary incontinence) is associated with worse prognosis. The findings of this study have implications for design of clinical trials. By the time diagnosis of probable MSA is made, the rate of progression has reached a plateau with minimal rate of increase in study instruments such as UMSARS I and II so that study design using probable MSA requires an unacceptably large number of subjects. A study design focused on an earlier stage of the disease (where change in status is occurring more rapidly) would require fewer subjects for a randomized clinical trial.

In comparing this study with the European prospective study (the only other prospective study on MSA), both studies found an identical duration of life (9.8 years). Both study observed that autonomic failure predicted worse outcome. The studies, together, indicated that MSA at an earlier stage changed more rapidly than at a late stage. Autopsy was done on few patients who expired but confirmed the diagnosis of MSA.

Publication

Natural history of multiple system atrophy in the USA: a prospective cohort study.
Low PA1, Reich SG2, Jankovic J3, Shults CW4, Stern MB5, Novak P6, Tanner CM7, Gilman S8, Marshall FJ9, Wooten F10, Racette B11, Chelimsky T12, Singer W13, Sletten DM13, Sandroni P13, Mandrekar J
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