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Consensus statement on the diagnosis of multiple system atrophy

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We report the results of a consensus conference on the diagnosis of multiple system atrophy (MSA). We describe the clinical features of the disease, which include four domains: autonomic failure/urinary dysfunction, parkinsonism and cerebellar ataxia, and corticospinal dysfunction. We set criteria to define the relative importance of these features. The diagnosis of possible MSA requires one criterion plus two features from separate domains. The diagnosis of probable MSA requires the criterion for autonomic failure/urinary dysfunction plus poor levodopa responsive parkinsonism or cerebellar ataxia. The diagnosis of definite MSA requires pathological confirmation.

Keywords: multiple system atrophy, parkinsonism, cerebellar ataxia, autonomic insufficiency, urinary dysfunction, glial cytoplasmic inclusions.

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Multiple system atrophy (MSA), a progressive neurodegenerative disease of undetermined etiology, occurs sporadically and causes parkinsonism and cerebellar, autonomic, urinary, and pyramidal dysfunction in many combinations [1–4]. The disease affects both sexes, usually beginning in middle age and progressing over intervals of 1 to 18 years, with a median survival of 9.3 years from the first symptom [5,6]. The parkinsonian features include bradykinesia with rigidity, postural instability, hypokinetic speech, and often tremor, usually with a poor or unsustained response to chronic levodopa therapy. The cerebellar dysfunction consists of ataxia of gait, limb movements and speech, and disorders of extraocular movements [7]. Autonomic insufficiency results in orthostatic hypotension, often with an inadequate heart rate response to standing, male erectile dysfunction (MED), constipation, and decreased sweating [8,9]. Urinary symptoms include urgency, frequency, nocturia, incomplete bladder emptying, and incontinence [10]. The diagnosis of MSA requires primarily clinical assessment; however, a number of laboratory tests may help to support the diagnosis.

The neuropathological changes consist of a high density of glial cytoplasmic inclusions (GCIs) in association with degenerative changes in some or all of the following structures: putamen, caudate nucleus, globus pallidus, substantia nigra, locus ceruleus, inferior olives, pontine nuclei, cerebellar Purkinje cells, autonomic nuclei of the brainstem, and the intermediolateral cell columns and Onuf's nucleus in the spinal cord [11,12]. GCIs are ubiquitin-, tau- and a-synuclein-positive oligodendroglial inclusions [12].

Some efforts have been made to establish diagnostic criteria [4], but no consistent detailed guidelines have been developed. Accordingly, a consensus conference was convened on April 23 and 24, 1998 in Minneapolis, Minnesota, cosponsored by the American Autonomic Society and the American Academy of Neurology. The goal of the conference was to develop guidelines for the diagnosis of MSA. We achieved consensus on the items listed below and shown in Tables 1, 2, and 3. These guidelines have not yet been validated, and will almost certainly require further modification in the light of future experience.

Clinical domains

Autonomic and urinary dysfunction

Orthostatic hypotension (OH) may indicate autonomic failure and can be asymptomatic or symptomatic. When symptomatic, it typically occurs after the onset of MED and urinary symptoms. Symptoms of OH result from cerebral hypoperfusion, and syncope may occur. The consensus conference determined that the clinical diagnosis of probable MSA requires a reduction of systolic blood pressure by at least 30 mm Hg or of diastolic blood pressure by at least 15 mm Hg within 3 minutes of standing from the recumbent

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Table 1. Clinical domains, features, and criteria used in the diagnosis of MSA*

I. Autonomatic and urinary dysfunction
  A) Autonomic and urinary features
    1. Orthostatic hypotension (by 20 mm Hg systolic or 10 mm Hg diastolic)
    2. Urinary incontinence or incomplete bladder emptying
  B) Criterion for autonomic failure or urinary dysfunction in MSA

Orthostatic fall in blood pressure (by 30 mm Hg systolic or 15 mm Hg diastolic) or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both

II. Parkinsonism
  A) Parkinsonian features
    1. Bradykinesia (slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions)
    2. Rigidity
    3. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
    4. Tremor (postural, resting, or both)
  B) Criterion for parkinsonism in MSA
    Bradykinesia plus at least one of items 2 to 4

III. Cerebellar dysfunction
  A) Cerebellar features
    1. Gait ataxia (wide based stance with steps of irregular length and direction)
    2. Ataxic dysarthria
    3. Limb ataxia
    4. Sustained gaze-evoked nystagmus
  B) Criterion for cerebellar dysfunction in MSA
    Gait ataxia plus at least one of items 2 to 4

IV. Corticospinal tract dysfunction
  A) Corticospinal tract features
    1. Extensor plantar responses with hyperreflexia
  B) Corticospinal tract dysfunction in MSA: no corticospinal tract features are used in defining the diagnosis of MSA

*A feature (A) is a characteristic of the disease and a criterion (B) is a defining feature or composite of features required for diagnosis.

position. Frequently this is accompanied by an inadequate increase in heart rate (less than 10 beats per minute). We note that this is a more pronounced degree of OH than established previously [4]. MED appears early and affects virtually all male patients with MSA, but the symptom has

Table 2. Diagnostic categories of MSA*

I. Possible MSA: One criterion plus two features from separate domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence only one additional feature is required).

II. Probable MSA: Criterion for: autonomic failure/urinary dysfunction plus poor levodopa-responsive parkinsonism or cerebellar dysfunction.

III. Definite MSA: Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways.

*The features and criteria for each clinical domain are shown in Table 1.

Table 3. Exclusion criteria for the diagnosis of MSA

I. History
  Symptomatic onset under 30 years of age
  Family history of a similar disorder
  Systemic diseases or other identifiable causes for features listed in Table 1
  Hallucinations unrelated to medication

II. Physical examination
  DSM criteria for dementia
  Prominent slowing of vertical saccades or vertical supranuclear gaze palsy*
  Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction

III. Laboratory Investigation
  Metabolic, molecular genetic, and imaging evidence of an alternative cause of features listed in Table 1

*In practice, MSA is most frequently confused with Parkinson's disease or progressive supranuclear palsy (PSP) [25]. Mild limitation of upward gaze alone is nonspecific, whereas a prominent (>50%) limitation of upward gaze or any limitation of downward gaze suggests PSP. Before the onset of vertical gaze limitation, a clinically obvious slowing of voluntary vertical saccades is usually easily detectable in PSP and assists in the early differentiation of these two disorders [26].

low specificity. Urinary frequency, urgency, incontinence, or incomplete bladder emptying also occur early and commonly.

Parkinsonism

The majority of MSA patients develop parkinsonian features at some stage of the disorder. All these patients have bradykinesia; rigidity, postural instability, and tremor also often occur. The tremor is usually irregular and postural, often incorporating myoclonus. A classical pill-rolling parkinsonian rest tremor is uncommon. The parkinsonism in MSA can be asymmetric. The dysarthria is mainly hypokinetic, often mixed with other components [13]. The parkinsonian features usually respond poorly to chronic levodopa therapy; however, up to 30% of patients show a clinically significant response to levodopa therapy at some time in the course, but the response is usually sustained for less than five years [5,14,15]. These are the most challenging patients for accurate diagnosis.

Cerebellar dysfunction

Ataxia of gait, the most common cerebellar feature of MSA, often occurs accompanied by dysarthria, limb ataxia, and sometimes gaze-evoked nystagmus and ocular dysmetria. A common finding is saccadic pursuit movements. The dysarthria in patients with predominantly cerebellar dysfunction is mainly ataxic, often mixed with other components [13].

Corticospinal dysfunction

Extensor plantar responses with hyperreflexia occur in about 50% of MSA patients. Corticospinal signs can contribute to the diagnosis, but are less important than abnormalities in the other domains.

Response to levodopa

Levodopa responsiveness should be tested by administering escalating doses (with a peripheral decarboxylase inhibitor) over a 3-month period up to at least 1 g per day (if necessary and if tolerated). A positive response is defined as clinically significant improvement. This should be demonstrated by objective evidence such as an improvement of 30% or more on part III (motor examination) of the Unified Parkinson's Disease Rating Scale [16].

Laboratory investigations

Autonomic function tests, sphincter electromyography (EMG), and neuroimaging may be used to support the diagnosis, and neuroimaging is helpful in excluding other conditions. The abnormalities described below have been defined principally in clinically well-established cases rather than in the early stages of the disease. In the early stages, the tests may give equivocal results. We consider it premature to incorporate laboratory results into the entirely clinical guidelines that we established, but envision the future development of "Laboratory Supported" diagnostic categories.

Assessment of autonomic function can be assisted by a comprehensive battery that evaluates the distribution and severity of sudomotor, cardiovagal, and sympathetic adrenergic deficits [17,18]. Autonomic function tests may help separate MSA from Parkinson's disease and from idiopathic cerebellar degenerations [8].

Sphincter EMG can be useful in the diagnosis of MSA. Analysis of individual motor unit potentials recorded from the external anal sphincter usually shows changes indicating chronic reinnervation, with markedly prolonged motor units [10,19].

Magnetic resonance imaging (MRI) can assist the evaluation by detecting abnormalities of striatum, cerebellum, and brainstem, but can be normal in up to 20% of cases [20]. Striatal abnormalities may include putaminal atrophy, slit-like signal change at the posterolateral putaminal margin, and hypointensity of the putamen relative to the globus pallidus [21]. Infratentorial abnormalities include cerebellar and pontine atrophy, and signal change in the pons and middle cerebellar peduncles [22]. Studies are in progress to evaluate the utility of magnetic resonance spectroscopy, positron emission tomography, and single photon emission tomography.

Diagnostic categories

We established three diagnostic categories reflecting differing levels of certainty: definite, probable, and possible. The diagnosis of definite MSA can only be made after neuropathological examination of the central nervous system revealing the characteristic density and distribution of GCIs and degenerative changes outlined above. The diagnosis of probable or possible MSA can be made using different combinations of clinical domains, criteria, and features, as indicated in Tables 1 and 2. Exclusion criteria are shown in Table 3.

Terminology

MSA is a distinct clinicopathological entity. The term should not be used to describe other neurodegenerative diseases affecting multiple systems. The use of confusing terms such as "multisystem degeneration" for MSA is inappropriate and now should be discouraged. We recommend designating patients as having MSA-P if parkinsonian features predominate or MSA-C if cerebellar features predominate [23,24]. These terms are intended to replace the striatonigral degeneration (SND) and sporadic olivopontocerebellar atrophy (sOPCA) types of MSA, respectively. The term Shy Drager syndrome has been widely misused, and is no longer useful.

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