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Review

Diagnosis of multiple system atrophy

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ABSTRACT

Multiple system atrophy (MSA) may be difficult to distinguish clinically from other disorders, particularly in the early stages of the disease. An autonomic-only presentation can be indistinguishable from pure autonomic failure. Patients presenting with parkinsonism may be misdiagnosed as having Parkinson disease. Patients presenting with the cerebellar phenotype of MSA can mimic other adult-onset ataxias due to alcohol, chemotherapeutic agents, lead, lithium, and toluene, or vitamin E deficiency, as well as paraneoplastic, autoimmune, or genetic ataxias. A careful medical history and meticulous neurological examination remain the cornerstone for the accurate diagnosis of MSA. Ancillary investigations are helpful to support the diagnosis, rule out potential mimics, and define therapeutic strategies. This review summarizes diagnostic investigations useful in the differential diagnosis of patients with suspected MSA. Currently used techniques include structural and functional brain imaging, cardiac sympathetic imaging, cardiovascular autonomic testing, olfactory testing, sleep study, urological evaluation, and dysphagia and cognitive assessments. Despite advances in the diagnostic tools for MSA in recent years and the availability of consensus criteria for clinical diagnosis, the diagnostic accuracy of MSA remains sub-optimal. As other diagnostic tools emerge, including skin biopsy, retinal biomarkers, blood and cerebrospinal fluid biomarkers, and advanced genetic testing, a more accurate and earlier recognition of MSA should be possible, even in the prodromal stages. This has important implications as misdiagnosis can result in inappropriate treatment, patient and family distress, and erroneous eligibility for clinical trials of disease-modifying drugs.

1. Introduction

Multiple system atrophy (MSA) is the most rapidly progressive of the synucleinopathies, a group of disorders characterized by the abnormal deposition of the protein α-synuclein (αSyn) in the central and peripheral autonomic nervous system (Roncevic et al., 2014; Wenning et al., 2013). While in patients with Parkinson disease (PD) and dementia with Lewy bodies (DLB) αSyn predominantly accumulates in neurons forming Lewy bodies and Lewy neurites, in patients with MSA it accumulates mostly in oligodendroglial cells forming glial cytoplasmic inclusions (GCI). A significant percentage of patients with MSA present with genitourinary dysfunction and orthostatic hypotension (OH) due to dysfunction of the autonomic nervous system, frequently combined with a history suggesting rapid eye movement (REM) sleep behavior disorder (RBD). Within a few years patients go on to develop balance, speech and coordination abnormalities that progress fairly rapidly. Depending on their initial predominant motor deficits, MSA is sub-classified into a parkinsonian (MSA-P) and a cerebellar phenotype (MSA-C) (Quinn, 2015). Age at onset, prevalence of cardiovascular autonomic dysfunction, sleep disorders, and retinal abnormalities are similar in both phenotypes (Mendoza-Santiesteban et al., 2015; Palma et al., 2015; Roncevic et al., 2014). Specific neuroimaging markers differ between the cerebellar and parkinsonian phenotypes (Deguchi et al., 2015; Huppertz et al., 2016; Lee et al., 2015), as well as the degree of sudomotor dysfunction which may be more severe in patients with MSA-P (Coon et al., 2017) and urogenital dysfunction which may occur earlier in patients with MSA-C (Zheng et al., 2017).

Patients with MSA have a mean age at onset of 55–60 years, and an average survival from the onset of motor symptoms of 8–9 years, although some pathology-proven cases survived > 15 years (Fanciulli and Wenning, 2015; Petrovic et al., 2012).

MSA may be difficult to distinguish clinically from other disorders, particularly in patients at the early stages of the disease. An autonomic-only presentation can be indistinguishable from pure autonomic failure (PAF) (Kaufmann et al., 2017b; Muppidi and Miglis, 2017). Patients presenting with parkinsonism may be misdiagnosed as PD. The reverse also occurs; approximately 20% of patients with a clinical diagnosis of MSA turn out to have PD or DLB at autopsy (Koga et al., 2015). Patients presenting with the cerebellar phenotype can mimic other adult-onset ataxias due to alcohol, chemotherapeutic agents, lead, lithium, and

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toluene, or vitamin E deficiency, as well as paraneoplastic, autoimmune, or genetic ataxias (e.g., spinocerebellar ataxias, fragile X–associated tremor ataxia syndrome, or late-onset Friedreich ataxia) (Klockgether, 2010; Lin et al., 2016). Misdiagnosis can result in inappropriate treatment, patient and family distress, and erroneous eligibility for clinical trials.

The accurate clinical diagnosis of MSA is based on a careful medical history and meticulous neurological examination. Ancillary investigations are helpful to support the diagnosis, rule out potential mimics, and define therapeutic strategies. This review summarizes diagnostic investigations useful in the diagnosis of MSA.

2. Clinical evaluation

A detailed clinical evaluation, including a medical history (Goldstein and Cheshire, 2017b), physical, and neurological examinations with special attention to gait, coordination and muscle tone, is the most important step in the evaluation of a patient with suspected MSA. The medical history should include questions about the onset and progression of motor symptoms as well as non-motor features including symptoms of cardiovascular, gastrointestinal, genitourinary, and sudomotor dysfunction; special attention should be paid to sleep disorders, the presence of cognitive, mood and behavioral problems, dysphagia, and visual abnormalities. Response to anti-parkinsonian medications, particularly levodopa, is usually sub-optimal and often transient (Calandra-Buonaura et al., 2016). Cold hands and feet are a typical feature of the disease (Asahina et al., 2013). A bluish discoloration of the feet is frequently seen in wheelchair-bound patients, probably due to venous stasis (Fig. 1A).

2.1. Non-motor signs and symptoms

All patients with MSA have gastrointestinal, cardiovascular, urogenital and thermoregulatory abnormalities but the severity of symptoms varies among patients (Fanciulli and Wenning, 2015; Roncevic et al., 2014). Indeed, the diagnosis of probable or possible

Table 1
Current consensus criteria for the diagnosis of multiple system atrophy.
Adapted from (Gilman et al., 2008).

Criteria for definite MSA include neuropathological findings during postmortem examination of:
a) Widespread and abundant cerebral α-synuclein–positive glial cytoplasmic inclusions
b) Neurodegenerative changes in striatonigral or olivopontocerebellar region

Criteria for probable MSA include a sporadic progressive adult (> 30 years old)–onset disease characterized by:
a) Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, *and*
b) Poorly levodopa-responsive Parkinsonism (bradykinesia with rigidity, tremor or postural instability), *or*
c) A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction)

Criteria for possible MSA include a sporadic progressive adult (> 30 years old)–onset disease characterized by:
a) Parkinsonism (bradykinesia with rigidity tremor or postural instability), *or*
b) Cerebellar syndrome (gait ataxia with cerebellar dysarthria limb ataxia or cerebellar oculomotor dysfunction), *and*
c) At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency frequency or incomplete bladder emptying erectile dysfunction in males or significant orthostatic BP decline that does not meet the level required in probable MSA), *and*
d) At least one of the following features:

- Babinski sign with hyperreflexia
- Stridor
- Rapidly progressive Parkinsonism
- Poor response to levodopa
- Postural instability within 3 years of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 year of motor onset
- Atrophy on MRI of putamen middle cerebellar peduncle, pons or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem or cerebellum
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

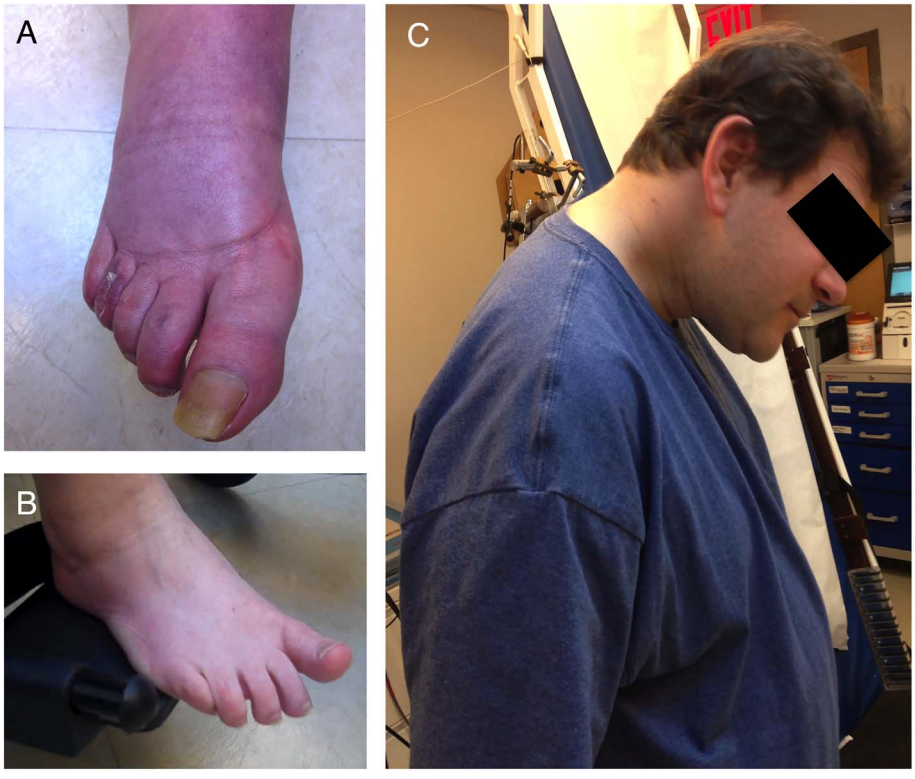

Fig. 1. A. Bluish discoloration in the foot of a patient with MSA-C. B. “Striatal toe”, spontaneous extensor toe response in a patient with MSA-C. C. Antecollis in a patient with MSA-P.