Parkinsonism and Related Disorders xxx (2015) 1–4

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Multiple system atrophy-mimicking conditions: Diagnostic challenges

Han-Joon Kim [a], Maria Stamelou [b, c], Beomseok Jeon [a, *]

[a] Department of Neurology and Movement Disorder Center, Parkinson Study Group, and Neuroscience Research Institute, College of Medicine, Seoul National University, 101 Daehakro, Chongno-gu, Seoul, 110-744, Republic of Korea
[b] Department of Neurology, Philipps Universität, Marburg, Germany
[c] Second Department of Neurology, Attikon University Hospital, University of Athens, Rimini 1, 12462, Athens, Greece

ARTICLE INFO

Article history:
Received 29 August 2015
Accepted 1 September 2015

Keywords:
Multiple system atrophy (MSA)
Diagnosis
Neurodegenerative disorders
Genetic disorders
Look-alikes

ABSTRACT

Multiple system atrophy (MSA) is a relentless progressive disorder without effective treatment. Its accurate diagnosis is important for the management of individual patients and for the development of new therapeutic strategies. However, there are many disorders which can mimic MSA (so-called 'MSA look-alikes'), and the true rate for over- or under-diagnoses of MSA is not known, especially during the early course of disease when the disease is not fully developed yet. Herein, the authors review the neurodegenerative, genetic, and immunologic conditions that can mimic MSA and thus be part of the differential diagnosis of MSA. Clinicians should be aware of these conditions and be able to differentiate them by clinical features and laboratory findings.

1. Introduction

Multiple system atrophy (MSA) is an adult-onset sporadic neurodegenerative disorder characterized by any combination of parkinsonism, cerebellar ataxia, and autonomic failure [1]. MSA is a relentlessly progressive disorder with a mean survival of 6–10 years [2], and there still is no disease-modifying therapy. As in other neurodegenerative disorders, a definite diagnosis of MSA is based on a postmortem confirmation [3]. In clinical practice, due to the lack of reliable biomarkers, clinicians have to rely on clinical diagnostic criteria which include clinical features and when necessary, neuroimaging features [3]. However, the accuracy of the clinical diagnosis of MSA is still unsatisfactory with the positive predictive value (PPV) even at the later stage ranging from 60 to 90% [4–6]. Although one study has shown that the PPV for the current clinical diagnostic criteria is 100%, despite a sensitivity of 18% [6], and another recent prospective study has shown an accuracy of 100% in 16 patients with probable MSA [2], these studies were performed in patients who came to autopsy with a diagnosis of MSA at death; thus, the true rate of over- or under-diagnoses of MSA in clinics is not known, especially during the early course of the disease. Improving the accuracy of the clinical diagnosis is of utmost importance for the management of individual patients and for the development of new therapeutic strategies.

2. Diagnostic challenges in MSA

Current clinical diagnostic criteria for MSA have several limitations which contribute to the suboptimal accuracy of the diagnosis [3,7]. First, both poorly levodopa-responsive parkinsonism and cerebellar ataxia can occur in numerous disorders other than MSA [8]. Furthermore, autonomic failure, the presence of which is a prerequisite for the diagnosis of MSA, is not specific to MSA and can occur even in otherwise healthy individuals [9,10]. Second, autonomic failure and motor symptoms do not develop simultaneously in many patients, which delays a correct diagnosis. Some MSA patients only develop autonomic failure early in the course of the disease and are misdiagnosed as primary autonomic failure (PAF) for years, whereas other patients develop autonomic failure up to 15 years after disease onset [11]. Third, recent studies have shown that patients with MSA can present with a wider range of clinical features than previously thought, including features considered atypical for MSA [7]. In this review, the authors primarily focus on conditions that can mimic MSA and thus be part of a differential diagnosis of MSA, especially during the early stage of the disease (Table 1).

* Corresponding author.
E-mail addresses: movement@snu.ac.kr (H.-J. Kim), mariastamelou@gmail.com (M. Stamelou), brain@snu.ac.kr (B. Jeon).

http://dx.doi.org/10.1016/j.parkreldis.2015.09.003
1353-8020/

2.1. Sporadic neurodegenerative disorders mimicking MSA

Definite diagnosis of a sporadic neurodegenerative disorder can be made only with postmortem pathologic examination of the brain tissue. There have been many studies reporting cases with clinical diagnosis of MSA for which postmortem pathological examinations revealed alternative pathologies. In some patients, more careful clinical and laboratory evaluations during their course might have helped to revise the diagnosis; however, in other cases, the clinical presentations were indistinguishable from that of MSA.

The disease most commonly confused with MSA-P is Parkinson disease (PD) [6]. Diagnosis of PD is not difficult when a patient presents with asymmetric parkinsonism, classic pill-rolling rest tremor, an excellent response to levodopa, and a good functional status after 4–5 years of the disease. However some PD patients may present with more symmetric parkinsonism without rest tremor, early postural instability, and a moderate response to levodopa, and in some cases also early autonomic dysfunction suggesting MSA-P [12]. If cerebellar ataxia is present, this may help the diagnosis of MSA, but this does not apply to cases without cerebellar symptoms. In these cases, sleep-disordered breathing and orofacial and neck dyskinesia with a low dose of levodopa favor a diagnosis of MSA. Conversely, some patients with MSA-P present with asymmetric parkinsonism and a good to excellent levodopa response, which can lead to a misdiagnosis of PD. Even motor fluctuations and levodopa-induced limb dyskinesia can rarely develop in patients with MSA [13].

Progressive supranuclear palsy (PSP) shares poorly levodopa-responsive parkinsonism, prominent axial symptoms, and early development of instability with MSA-P. Especially, patients with a parkinsonian variant of PSP (PSP-P) may present with normal eye movements initially [14], complicating the correct diagnosis when symptoms of autonomic failure are present. Although it has been reported that true autonomic dysfunction is uncommon in PSP-P [15], urinary incontinence due to reduced mobility can be present. PSP with prominent cerebellar ataxia ('PSP-C') may be misdiagnosed as MSA-C [5,16]. It has been shown that older age at onset, early falls, and supranuclear vertical gaze palsy without autonomic dysfunction within 2years of disease onset indicate a diagnosis of PSP-C [16]; however, PSP-C with autonomic dysfunction has been described [5]. Corticobasal degeneration, another tauopathy, also can present with the clinical features of MSA [4,5].

Dementia with Lewy bodies (DLB) shares poorly levodopa-responsive parkinsonism and autonomic dysfunction with MSA-P. According to the current diagnostic criteria, the most obvious features distinguishing DLB from MSA-P are the presence of dementia with fluctuating cognition and visual hallucinations, which are features not supporting a diagnosis of MSA [3]. However, recent studies have shown that cognitive dysfunction may occur in patients with MSA [17]. On the other hand, intriguingly, one recent study has shown that 19 out of 134 patients (14%) with a clinical diagnosis of MSA at death turned out to have a pathologic diagnosis of DLB rather than MSA [5]. Absent or mild cognitive impairment despite the pathology of DLB limited the correct diagnosis in those patients. The authors also raised the possibility that the abnormal findings in neuroimaging, which suggest a diagnosis of MSA, might have been overlooked by clinicians.

PD, PSP, and DLB are the major disorders that can be misdiagnosed as MSA-P. In addition, rare cases with motor neuron disease, especially primary lateral sclerosis, can be misdiagnosed as MSA-P due to pyramidal slowing and hyperreflexia [18].

Sporadic adult-onset ataxia of unknown etiology (SAOA), also known as idiopathic adult-onset cerebellar ataxia, is the most common among progressive ataxias in adults. Presumably, it is a heterogeneous group of diseases with various etiologies including genetic, inflammatory, immunologic, and metabolic factors. One study has shown that 24% of the patients diagnosed with SAOA evolve to MSA in 5 years [19]. MSA-C can be indistinguishable from

Table 1
MSA mimicking conditions.

Sporadic neurodegenerative	Parkinson disease
	Progressive supranuclear palsy
	Dementia with Lewy bodies
	(Corticobasal degeneration)
	Motor neuron disease
	Sporadic adult-onset ataxia of unknown etiology
	Primary autonomic failure
Genetic	Perry syndrome (*DCNT1* mutation)
	Hereditary spastic paraplegias
	Late-onset Huntington's disease
	SNCA multiplications
	Spinocerebellar ataxias
	Autosomal recessive cerebellar ataxias
	Fragile X tremor-ataxia syndrome (*FMR1* premutation)
	X-linked adrenoleukodystrophy (*ABCD1* mutation)
	Cerebrotendinous xanthomatosis (*CYP27A1* mutation)
	Mitochondrial disorders
	C9orf72 mutation
Immunologic/Inflammatory	Multiple sclerosis
	Paraneoplastic cerebellar degeneration
	Gluten ataxia
	Hashimoto's encephalopathy
	Anti-GAD ataxia
	System lupus erythematosus
	Sjögren's syndrome
	Neuro-Behçet's disease
	HIV infection
Others	Vascular parkinsonism
	Normal pressure hydrocephalus
	Alcoholic cerebellar degeneration
	Drug-induced cerebellar degeneration
	Prion disorder (genetic or sporadic)

Please cite this article in press as: H.-J. Kim, et al., Multiple system atrophy-mimicking conditions: Diagnostic challenges, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.09.003