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Cardiovascular autonomic dysfunction in MSA and Parkinson's disease: Similarities and differences

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ABSTRACT

In Parkinsons disease and multiple system atrophy (MSA), cardiovascular dysfunction may occur for a variety of reasons and may manifest itself through inappropriate changes and/or levels in blood pressure, heart rate and/or regional vascular perfusion in a range of situations. The early occurrence of orthostatic hypotension often leads to consideration of MSA, especially in the presence of other features of autonomic failure. Orthostatic hypotension, however, is increasingly recognised in PD, and especially with increasing age, severity of disease and as a result of drug therapy, sometimes for associated disorders. Investigation of cardiovascular autonomic dysfunction in Parkinsonism is therefore important for a variety of reasons, that include determining the precise diagnosis and in predicting prognosis. In Parkinsonian disorders, understanding the pathophysiological basis of the cardiovascular autonomic dysfunction aids targeting of therapy, improves management strategies and provides benefit for such patients.

1. Introduction

The cardiovascular system is influenced by a variety of factors that include the sympathetic and parasympathetic components of the autonomic nervous system. In Parkinson's disease (PD) and multiple system atrophy (MSA), cardiovascular dysfunction may occur for a variety of reasons and may manifest itself through inappropriate changes and/or levels in blood pressure, heart rate and/or regional vascular perfusion in a range of situations. Autonomic failure is an integral component of Parkinsonian syndromes where orthostatic (postural) hypotension is an important clue to underlying cardiovascular autonomic failure and in the recognition of these disorders. Many Parkinsonian patients also are on drugs that may have cardiovascular side effects. This brief review will describe and compare aspects of cardiovascular dysfunction resulting from autonomic impairment in PD and MSA.

2. Blood pressure control

Hypotension or hypertension may result from disruption of autonomic control. As organ function is dependent upon an adequate perfusion pressure, the symptoms arising from hypotension (such as syncope with head-up postural change) often are more prominent than those resulting from hypertension.

2.1. Hypotension

2.1.1. Orthostatic hypotension

A cardinal feature of failure of the sympathetic nervous system is orthostatic hypotension, defined by consensus as a fall in systolic blood pressure of >20 mm Hg, or in diastolic blood pressure >10 mm Hg, on either standing or head-up tilt to at least 60° within 3 min [1]. A drop of systolic blood pressure of >30 mm Hg has recently been suggested in patients with supine hypertension [2]. On assuming the upright posture, hypotension-induced hypoperfusion of the brain can result in dizziness, visual disturbances and impaired cognition that often precede loss of consciousness (Table 1). In MSA, symptoms of orthostatic hypotension are common, although syncope occurs in less than 50% [3]. With time symptoms may diminish for reasons that include improved cerebrovascular autoregulation [4]. There is a variety of non-cerebral symptoms associated with orthostatic hypotension that result from underperfusion of various organs, such as 'coat-hanger' pain in the back/shoulders [3]. In Parkinsonian patients the associated movement disorder may enhance the propensity to falls, from which injury may result. Many patients with PD have OH after 3 min of orthostasis [5], suggesting that tilting for longer than the recommended 3 min should be considered in order to detect delayed OH.

The presence of orthostatic hypotension does not separate MSA from other Parkinsonian syndromes or disorders where autonomic dysfunction occurs [6], which is the reason for the range of tests described in different autonomic disorders [7] (Table 2). Previous post-mortem studies emphasised the potential difficulties of an *in vivo* diagnosis and in separating PD from non-PD disorders, such as

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Table 1
Some of the symptoms resulting from orthostatic (postural) hypotension (Adapted from Mathias 2003).

Cerebral hypoperfusion
Dizziness
Visual disturbances
Blurred-tunnel
Scotoma
Greying out–blacking out
Colour defects
Loss of consciousness
Impaired cognition
Muscle hypoperfusion
Paracervical and suboccipital ('coat-hanger') ache
Lower back/buttock ache
Cardiac hypoperfusion
Angina pectoris
Spinal cord hypoperfusion
Renal hypoperfusion
Oliguria
Non-specific symptoms
Weakness, lethargy, fatigue
Falls

MSA, [8]. However, with the increasing amount of clinical research into Parkinsonian disorders and development of specialised autonomic centres, there are several autonomic and allied investigations and clinical pointers that enable an earlier probable diagnosis. One is orthostatic hypotension that may occur early in the course of MSA, as autonomic failure is a key component. Its presence leads to the consideration of this disorder [9], especially when there are additional non-cardiovascular features of autonomic failure [10]. Orthostatic hypotension, however, can occur in PD, especially with increasing age, severity of disease and as a result of drug therapy, and in some also before the hallmark motor phase of PD [11]. Therefore, depending on the individual, additional tests and information may be required before differentiating between MSA and PD. In PD, the reported prevalence and incidence of orthostatic hypotension varies considerably; ranging from rare [12] to high (42–58%) [10,13]. Whether the disparity in prevalence estimated reflects variations in the type of patient studied, the influence of factors that modify blood pressure control (*e.g.*, age, duration of the disorder and drug therapy), or differences in definitions and/or methods to evaluate orthostatic hypotension, is unclear [14]. Impaired mobility itself may contribute to autonomic dysfunction, as is known to occur, especially in elderly bed-bound patients [15]. A recent prospective study of MSA and PD confirmed that OH is almost invariably present in MSA; and it was also present in 42% with PD [10]. This study used the latest consensus statement for the diagnosis of MSA, *e.g.*, defined by featuring OH, and the typical diagnosis criteria of PD, *e.g.*, presence of the 3 cardinal features of PD (resting tremor, bradykinesia, and rigidity); autonomic failure was not required for PD entry but these patients were included. In a recent meta-analysis of 25 studies, a prevalence of OH of 30% in PD was reported with a large statistical heterogeneity between studies [16].

Table 2
Outline of cardiovascular autonomic investigations in autonomic failure (From Mathias & Bannister 2002).

Physiological	Head-up tilt (60°)[a]; Standing[a]; Valsalva manoeuvre[a]
	Pressor stimuli — isometric exercise[a], cutaneous cold[a], mental arithmetic
	Heart rate responses — deep breathing[a], hyperventilation[a], standing[a], head-up tilt[a], 30:15 ratio
	Liquid meal challenge
	Exercise testing
	Carotid sinus massage
Biochemical	Plasma noradrenaline — supine and head-up tilt or standing; urinary catecholamines; plasma renin activity and aldosterone
Pharmacological	Noradrenaline–α-adrenoceptors — vascular
	Isoprenaline–β-adrenoceptors — vascular and cardiac
	Tyramine — pressor and noradrenaline response
	Edrophonium — noradrenaline response
	Atropine — parasympathetic cardiac blockade

[a] Indicates screening tests used in our units.

2.2. Mechanisms of OH

The mechanisms and pathophysiological basis of orthostatic hypotension in MSA and PD are of relevance for diagnosis and importantly for determining which drugs are more likely to provide effective benefit (see Table 3). Regardless of the actual mechanisms, they will ultimately contribute to the inability to increase vascular resistance and/or cardiac output during orthostasis in these patients. Proposed mechanisms in PD include, central lesions in the upper brainstem, that affect postural control of blood pressure through baroreflex failure, and loss of sympathetic innervation, *e.g.*, post-ganglionic impairment, most noticeably in the heart [17], whereas in MSA only central lesions are considered the likely mechanisms. Baroreflex function (as indexed by the cardiovagal gain calculated during the Valsalva manoeuvre which provokes large changes in blood pressure) is similarly decreased in MSA and PD and even further in PD and MSA with OH [18]. In contrast, baroreflex sensitivity (calculated from spectral analysis of resting heart rate and systolic blood pressure) was reported to be lower in MSA but not in a group of PD patients including those with and without OH [19]. Multiple system atrophy and PD are characterised by deposition of abnormally phosphorylated α-synuclein. In PD, the aggregates are typically found in neurons as Lewy bodies, whereas in MSA α-synuclein is deposited predominantly in the form of oligodendroglial and neuronal cytoplasmic inclusions [20]. Alongside the hallmark degeneration of the substantia nigra in PD, Lewy bodies and cell loss are detected in: 1) autonomic regulatory areas such as the hypothalamus, parabrachial nucleus, intermediate reticular zone of the medulla, locus coeruleus and raphe; 2) pre-ganglionic parasympathetic regions, such as the Edinger–Westphal nucleus and dorsal vagal motor nuclei; 3) pre-ganglionic sympathetic neurons in the intermediolateral cell column, and 4) neurons in paravertebral and prevertebral autonomic ganglia [21]. Histological loss of neurons and Lewy body accumulation in sympathetic ganglia [22] and cardiac sympathetic denervation in several studies (see below) [23–25] further support peripheral autonomic system involvement in PD.

Oligodendroglial and neuronal cytoplasmic inclusions in MSA are associated with neuronal and myelin loss, astrocytosis and a marked microglial reaction most prominent in brain regions involved in motor and supraspinal autonomic control [26]. In particular, there is depletion of corticotrophin-releasing factor neurons in the pontine micturition area, cholinergic, glutamatergic and serotonergic neurons in the ventral medulla [27], serotonergic neurons in the ventrolateral

Table 3
Possible causes of orthostatic hypotension and autonomic dysfunction in a patient with Parkinsonian features (Adapted from Mathias 1996 and Mathias & Kimber 1999).

Side effects of anti-Parkinsonian therapy, including
L-dopa, bromocriptine, pergolide
The combination of L-dopa and COMT inhibitors (tolcapone)
The MAO 'b' inhibitor, selegiline
Coincidental disease causing autonomic dysfunction, *e.g.* diabetes mellitus
Coincidental administration of drugs for an allied condition
Antihypertensives
α-adrenoceptor blockers (for benign prostatic hypertrophy)
Vasodilators (for ischaemic heart disease)
Diuretics (for cardiac failure)
Sildenafil (for erectile failure)
Multiple system atrophy (Shy-Drager syndrome)
Parkinson's disease with autonomic failure
Diffuse Lewy body disease