Multiple system atrophy: new developments in pathophysiology and therapy

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Abstract

There have been substantial advances in the last five years in understanding the basic and clinical pathophysiology underlying multiple system atrophy (MSA). Identification of glial cytoplasmic inclusions has been the most important organizing principle for further elucidation of underlying mechanisms. Recently, several unexpected developments at the clinical level have been reported. In this article, we will focus on two of these: (1) the recognition that substantial autonomic function is retained in MSA but not modulated appropriately, and (2) a potent pressor effect from ingestion of water, which cannot be explained by currently understood physiologic and pathophysiologic mechanisms. In some patients, water has elicited a 50% increase in blood pressure and been more therapeutically effective than any available pressor drug. By careful coordination of the pressor effect of water and the depressor effect of carbohydrate-rich food, many patients with MSA can now have their blood pressure controlled without pharmacological intervention. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Enormous advances have been made during the last five years in understanding the basic and clinical pathophysiology underlying multiple system atrophy (MSA) [1,2]. The identification of glial cytoplasmic inclusions [3,4] provided an organizing principle that facilitated taxonomy and clarified the full spectrum of the disease and led to improvements in nomenclature [5,6] and efforts to develop diagnostic criteria for the disease [7,8]. Analysis of the biochemical composition of the glial cytoplasmic inclusions led to the recognition that α-synuclein deposition was a hallmark of the disease [9,10] and perhaps an important clue to etiology [11,12]. This is reviewed by Trojanowski elsewhere in this issue [13] and will not be further addressed in this article. At the clinical level, several unexpected developments have provided remarkable insights into the nature of the disease and its treatment, which will be discussed below. These have greatly altered the way we think about MSA, and the way we treat it.

2. Preserved autonomic function in MSA

Autonomic dysfunction was the organizing principle in most of the early literature on MSA [14,15]. Indeed, it took two decades of clinical experience to separate MSA from autonomic failure per se [16]. But the nature of the autonomic dysfunction did not fully emerge until the last five years in studies of the N1-nicotinic receptor antagonist, trimethaphan [17]. As a ganglionic blocker, trimethaphan results in the disengagement of both sympathetic and parasympathetic nervous system functions. The drug thus provides a powerful model of acute autonomic failure. When the effects of trimethaphan administration were carefully compared to the clinical presentation of MSA, striking differences emerged.

Trimethaphan given intravenously to normal subjects causes a rise in heart rate and a fall in blood pressure [17]. Skin temperature in the extremities rises. Intestinal motility and bowel sounds cease. Bowel movements do not occur. Sweating stops. Vasodilatation results in injected conjunctivae. Horripilation (gooseflesh) disappears. Sinus arrhythmia is lost, and with it the normal power spectral analysis pattern of heart rate.

The picture emerging from this model is very different

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from the presentation of MSA. In patients with MSA, supine blood pressure is often significantly raised, although it falls with upright posture [18]. Heart rate is near normal in the supine state and may rise variably with upright posture. The extremities are cool, sometimes quite cold on physical examination. Intestinal motility may be reduced but bowel sounds are present, and constipation is usually only marginal. Sweating is altered but cold sweating may occur in the extremities. Conjunctival injection does not occur. Sometimes horripilation is clearly visible. Sinus arrhythmia is generally lost, but this is about the only one of the key autonomic features of trimethaphan which is characteristic of autonomic failure.

Because of this disparity, Shannon and Jordan [19,20] administered trimethaphan to patients with MSA and to patients with other forms of autonomic failure. The purpose was to test the hypothesis that residual autonomic mechanisms might still be active in such patients. If complete autonomic failure were present, then the administration of ganglionic blockade should elicit little additional effect and might seem to be without pharmacologic activity. On the other hand, to the extent that ongoing sympathetic and parasympathetic actions were present, their antagonism by trimethaphan should produce the typical pharmacological profile.

The magnitude of the response to trimethaphan in a variety of autonomic disorders was unexpectedly large. The least effect was found in patients with pure autonomic failure, loss of sinus arrhythmia, and profoundly low plasma norepinephrine levels. But even here, some fall in blood pressure was almost always seen. The greatest effect was found in patients with MSA. Indeed the supine hypertension characteristic of MSA was rapidly replaced by a dramatic fall in blood pressure; this occurred at very low doses of trimethaphan which had little effect on supine blood pressure in normal subjects. The heart rate changes were comparatively small. Associated with these effects was a dramatic fall in plasma norepinephrine from near normal levels to levels less than 25% of the normal, an effect which developed within a few minutes. Taken together, these findings indicated the presence of ongoing autonomic activation.

There has been recognition for many years that a dichotomy existed between ‘central autonomic failure’ represented by movement disorders with autonomic involvement on the one hand, and ‘peripheral autonomic failure’ represented by pure autonomic failure on the other. In the former, it was initially assumed that an anatomically present autonomic system failed to be engaged by the central nervous system and that autonomic function largely ceased for this reason. In the latter, it was believed that the peripheral autonomic nervous system itself was the target of degeneration. Careful recent study confirms this view of pure autonomic failure [21] where Lewy bodies can be identified in a variety of peripheral autonomic neural tissues and in the heart.

The situation in movement disorder associated dysautonomia has proved to be more complex. In Parkinson’s disease, definitive evidence of peripheral autonomic involvement has emerged [22], adumbrated by the early recognition that plasma renin activity, a marker of sympathetic nervous system function, was low in Parkinson’s disease [23]. Studies with imaging of the noradrenergic nervous system in the heart suggest largely normal innervation in MSA but a contrasting loss of such innervation in Parkinson’s disease. The results of the trimethaphan studies demonstrate the remarkable functional importance of this finding in patients with MSA.

A plausible interpretation of these results is that in MSA, the peripheral autonomic nervous system is ‘autonomous’ in the truest sense: it is no longer controlled by central cardiovascular regulatory mechanisms but, more importantly, is not shut down entirely but rather continues to function constitutively. This interpretation would suggest that supine hypertension in MSA is supported by a sympathetic activation level that is too high for the supine posture. Yet while this constitutive sympathetic activation may be too high for the supine posture, it may well be inadequate to support the upright posture, as the latter stimulus requires a substantial step-up in sympathetic activation.

The documentation of the powerful autonomic control being exerted in MSA provides an enticing target for the development of improved drug therapy in blood pressure control. If the autonomic ganglia are targets of pharmacological intervention, then altered sympathetic activity might be achieved by a range of agents which enhance nicotinic transmission (nicotine, neostigmine) or increase synaptic norepinephrine content. The latter might be achieved by β-2 agonists which promote norepinephrine release, monoamine oxidase inhibitors which reduce breakdown of norepinephrine, and norepinephrine transporter antagonists which may block norepinephrine removal from the synapse [22]. Whether these agents will be useful from a practical standpoint will require systematic and long-term studies.

3. An unexpected therapeutic tool

Over the years a number of MSA patients had described improvement in upright blood pressure on ingestion of water. Traditional physiology texts do not provide a rationale for a pressor effect of water drinking in individuals who are not dehydrated. Indeed most of the attention of blood pressure investigators has been aimed at examining and understanding the long-term effects of dietary sodium on arterial pressure. It was therefore surprising when, under controlled conditions, we assessed the effect of tap water on blood pressure following oral ingestion (Fig. 1).

Water was given to MSA patients in a dosage of 16 oz., ingested fairly rapidly over a period of 2–3 min [24]. In response to this, blood pressure became detectably higher within 10 min and climbed to a maximal pressure increase.
of about 50 mmHg, peaking at approximately 25 min following ingestion. From that pressor effect, a gradual decline occurred that brought blood pressure back to baseline over the next 45 min. While some patients had responses smaller than 50 mmHg, in others blood pressure rose more than 75 mmHg (Fig. 2). The magnitude of this response was astonishing. Indeed, it was greater than that observed with commonly used doses of any other pressor agent in MSA [25]). The effect was present in the supine posture and also in the seated posture, and translated into a significant increase also in the standing blood pressure. In healthy young subjects the pressor effect of water was not observed, although a significant increase in plasma norepinephrine was seen. However, in older normal subjects a mean increase in blood pressure of 11 mmHg was seen.

To address the mechanism of this unexpected effect of water, trimethaphan was administered to determine if the effect was dependent on the integrity of autonomic function. In the presence of trimethaphan, no effect of water on blood pressure was observed. Administration of a comparable volume of 5% dextrose solution intravenously did not duplicate the pressor effect of oral water. Furthermore, administration of cold (4°C) and warm (37°C) water was effective to the same degree as water at room temperature. The water response correlated with response to the α2-adrenoreceptor antagonist, yohimbine (Fig. 3). These data suggest that sympathetic activation is somehow elicited by oral water but that this is most dramatically manifested with impairment in central autonomic control as in the case of MSA.

It is remarkable that this effect of water had been missed by physicians for so many years, but probably we were so influenced by our physiology training that we could not see this striking anomaly. However, once recognized, the effect of water has proved to be a significant therapeutic advance. Its value vis-a-vis other drugs lies in the potency of its action, the lack of major side effects, the rapidity of its onset, and, since supine hypertension is often a limiting factor in therapy of patients with MSA, the relatively fast return of blood pressure to normal. The depressor effect of food, especially carbohydrates, has long been recognized in MSA. Now with the recognition of the pressor effect of water, a simple and patient-controlled approach to blood

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**Fig. 1.** Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) after patients with MSA (top) and pure autonomic failure (bottom) drank 480 ml of tap water. Patients started drinking at 0 min. The blood pressure increase was evident within 5 min of drinking water, reached a maximum after approximately 30–35 min, and was sustained for more than 60 min.

**Fig. 2.** Changes in systolic blood pressure (SBP) in two MSA patients during a baseline study (−trimeth) and then during ganglionic blockade with trimethaphan (+trimeth). Both subjects had a profound increase in systolic blood pressure with water drinking in the absence of ganglionic blockade, while the pressor response was almost completely abolished during the infusion. Patients started drinking at 0 min.
pressure management is possible. Our experience so far suggests that many patients need no other therapy for the control of blood pressure than the judicious dosing of food and water. Careful further studies will be required in order to elucidate the precise mechanism underlying the effect of water, but action through gastrointestinal stretch receptors or osmoreceptors must be addressed in future investigations.

References