Clinical Autonomic Research (2019) 29:267–275
https://doi.org/10.1007/s10286-019-00605-z

REVIEW ARTICLE

Immune and autonomic nervous system interactions in multiple sclerosis: clinical implications

Mario Habek[1,2]

Received: 31 January 2019 / Accepted: 28 March 2019 / Published online: 8 April 2019

Abstract

Multiple sclerosis is characterized by a wide spectrum of clinical manifestations, among which dysfunction of the autonomic nervous system represents an important cause of multiple sclerosis-related disability. The aim of this review is to provide an overview of autonomic dysfunction in people with multiple sclerosis, and to discuss the interactions between the immune and autonomic nervous systems and the effects of these interactions on various aspects of multiple sclerosis. Autonomic dysfunction in people with multiple sclerosis can be demonstrated clinically and on a molecular level. Clinically, it can be demonstrated by measuring autonomic symptoms with the Composite Autonomic Symptom Score (COMPASS-31), and neurophysiologically, with different autonomic nervous system tests. Both symptomatic and objectively determined autonomic dysfunction can be associated with increased risk of multiple sclerosis disease activity. Further supporting these clinical observations are molecular changes in immune cells. Changes in the sympathetic autonomic system, such as different expression of dopaminergic and adrenergic receptors on immune cells, or modulation of the cholinergic anti-inflammatory pathway over different subunits of the nicotinic acetylcholine receptor in the peripheral immune system, may mediate different effects on multiple sclerosis disease activity.

Keywords Multiple sclerosis · Autonomic nervous system · Cardiovascular autonomic reflexes · Sudomotor function

Introduction

Inflammation and neurodegeneration are common underlying processes in multiple sclerosis (MS), triggered by a pathological activation of the immune system [1]. MS is characterized by a wide spectrum of clinical manifestations, among which dysfunction of the autonomic nervous system (ANS) represents an important cause of MS-related disability. The reason for this is a variety of clinical manifestations which are consequences of end-organ dysfunction innervated by ANS [2]. It has recently been suggested that pathological interactions between the immune and the autonomic systems may fail to trigger anti-inflammatory mechanisms that are essential in preventing repeated inflammatory attacks, a key pathogenic feature of MS [3]. Based on limited available data, it can be speculated that both sympathetic and parasympathetic ANS function and/or dysfunction exert an influence on inflammatory/anti-inflammatory and neurodegenerative pathways in MS.

The aim of this review is to provide an overview of ANS dysfunction in people with MS (pwMS), and to discuss the interactions between the immune and autonomic nervous systems and the consequences of these interactions with regard to various aspects of MS.

Autonomic nervous system abnormalities in multiple sclerosis

In general, ANS research can be divided into research regarding patient-reported symptoms (usually using different questionnaires) and assessment of ANS function/dysfunction in the laboratory. One of the most commonly used questionnaires for the investigation of ANS symptoms is the Autonomic Symptom Profile, which comprises 169 questions and assesses 11 domains of autonomic function [4]. Because of several problems with this instrument, a shortened version,

✉ Mario Habek
mhabek@mef.hr

[1] Department of Neurology, Referral Center for Autonomic Nervous System Disorders, University Hospital Center Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia

[2] School of Medicine, University of Zagreb, Zagreb, Croatia

the Composite Autonomic Symptom Score (COMPASS-31) questionnaire, was developed (31 questions in 6 autonomic domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupillomotor), which provides an autonomic symptom score ranging from 0 to 100 [5]. As COMPASS-31 was found to be suitable for widespread use in autonomic research and clinical practice, it has been validated in several languages, and we recently validated the Croatian version of COMPASS-31 for use in pwMS [6]. We found a significant correlation between the Expanded Disability Status Scale (EDSS) and the COMPASS-31 total score, as well as significant differences between MS phenotypes [clinically isolated syndrome (CIS), relapsing–remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS)] in the COMPASS-31 total score, with the lowest score for people with CIS (pwCIS) and highest for people with PPMS (pwPPMS). A Portuguese study showed alterations in at least one autonomic symptom domain of the COMPASS-31 in 97.1% of participants, with gastrointestinal and pupillomotor domains being the most frequently affected [7]. Finally, a study by Cortez and colleagues performed in a small group of people with relapsing–remitting MS (pwRRMS) found no significant relationship between COMPASS-31 and EDSS or disease duration, but found significant correlations with quality of life [8]. The validity of the COMPASS-31 is further supported by a recent study showing that people with laboratory-confirmed ANS dysfunction score higher on certain domains of the scale [9]. Taking into account all these studies, we can conclude that COMPASS-31 is an important tool for the detection of ANS symptoms in pwMS and that it can detect ANS symptoms in different MS phenotypes, including the earliest stages of MS, as well as in patients with a low level of disability.

Assessment of ANS function in the laboratory is another aspect of ANS research, and in recent years there has been an upsurge in laboratory ANS investigations in pwMS (Table 1). In general, the most extensively investigated part of the ANS is the cardiovascular autonomic system, due to its availability for testing. Studies using cardiovascular autonomic testing have shown that laboratory-confirmed parasympathetic nervous system dysfunction exists in 0–55% and sympathetic nervous system dysfunction in 0–61% of pwMS (Table 1). The main problem with the laboratory examination of ANS function is that different tests are used in different laboratories, making comparisons between studies very difficult. A good example of the latter is a study by Acevedo et al. showing parasympathetic nervous system dysfunction in 43% of pwMS when using heart rate response to the Valsalva maneuver, and 30% when using respiratory sinus arrhythmia [10]. Another factor that can explain observed differences in the frequency of autonomic dysfunction (AD) is differences in patient characteristics (age, disease duration, level of disability, MS phenotype) among patient populations enrolled in different studies. An example of results that vary by MS phenotype is a study by de Seze et al., which showed sympathetic nervous system dysfunction in 0% of pwRRMS, 20% of pwSPMS and 32% of pwPPMS [11]. The only way to overcome these problems is to use a standardized battery of ANS tests corrected for age and sex in a strictly defined population of pwMS. Initial attempts to overcome this problem in pwMS involved the use of a scoring method for each autonomic test, with 0 points if the test result was normal, 1 point if the result was borderline, and 2 points for abnormal results [12]. However, this method again could use many different tests and thus make comparisons between studies difficult. Another approach was the development of the Composite Autonomic Scoring Scale (CASS). CASS is a 10-point scoring scale that uses a standardized battery of ANS tests including heart rate response to deep breathing and Valsalva maneuver as measures of parasympathetic nervous system function, blood pressure response to Valsalva maneuver and tilt-table test as measures of sympathetic nervous system function, and the quantitative sudomotor axon reflex test (QSART) as a measure of sudomotor function [13]. The maximum CASS score is 10, with 4 points for adrenergic and 3 points each for sudomotor and cardiovagal failure. Although CASS was initially developed for patients with multiple system atrophy, Parkinson's disease and autonomic neuropathy, it has been successfully used in pwMS as well. We used CASS in a large, well-defined cohort of people with clinically isolated syndrome (pwCIS) and found that it could detect AD in a large proportion of patients, namely parasympathetic dysfunction in 5%, sympathetic in 42.6% and sudomotor in 32.7% of participants [14]. In a subsequent study we used CASS in a cohort of pwRRMS and progressive MS (PMS), and found that the type of multiple sclerosis (RRMS or PMS), corrected for age, sex and disease duration, was a statistically significant predictor of CASS value [15]. Furthermore, both disease duration and EDSS correlated positively with total CASS. These studies indicate that CASS is a valuable tool for evaluating ANS dysfunction in pwMS, and enables comparison of results across different studies.

Interestingly, in structural disorders of the ANS such as MS, there is a large discrepancy between patient-reported symptoms and laboratory ANS findings. Studies have shown that in up to a third of cases, even patients with severe sympathetic dysfunction (orthostatic hypotension with a decrease in systolic blood pressure more than 60 mmHg from baseline during a head-up tilt-table test) can be completely asymptomatic during the head-up tilt-table test [16]. Similarly, one study showed no significant association between the presence of symptoms of AD and laboratory-confirmed autonomic damage [17].

Table 1 Studies investigating different types of autonomic dysfunction in patients with multiple sclerosis using different autonomic tests

References	Number of participants	MS phenotype	Sympathetic dysfunction	Parasympathetic dysfunction	Sudomotor dysfunction
Noronha et al. [31]	60	NR	NR	NR	42%[a]
Mutani et al. [32]	10	NR	NR	40%[b]	NR
Senaratne et al. [33]	11	NR	NR	55%[b]	NR
	19	NR	16%[d]	21%[c]	NR
Pentland et al. [34]	50	NR	0%[e]	8%[c], 30%[b]	NR
Yokota et al. [35]	28	RRMS	NR	NR	75%[f]
Anema et al. [36]	34	NR	13%[e] (out of 30 patients)	36%[b]	NR
Thomaides et al. [37]	10	SPMS	0%[g]	0%[b,c]	NR
Gutrecht et al. [38]	29	NR	NR	NR	59%[f]
Vita et al. [17]	40	NR	0%[e]	18%[b]	NR
Elie and Louboutin [39]	70	RRMS 41, PMS 29	NR	NR	94%[f]
Linden et al. [40]	30	NR	14%[e] (out of 22 patients)	10%[b]	67%[f]
Caminero et al. [41]	63	NR	NR	NR	41%[f]
Linden et al. [42]	20	NR	5%[g]	25%[b]	75%[f]
Nasseri et al. [22]	20	RRMS	NR	20%[b]	NR
Flachenecker et al. [12]	40	RRMS, SPMS	8%[e]	3%[c], 10%[b]	NR
Acevedo et al. [10]	40	RRMS 30, PMS 10	38%[e]	43%[c], 30%[b]	NR
de Seze et al. [11]	25	RRMS	0%[e]	0%[h]	30%[f]
	25	SPMS	20%[e]	12%[h]	48%[f]
	25	PPMS	32%[e]	12%[h]	48%[f]
Merkelbach et al. [43]	54	RRMS	22%[e]	2%[c], 22%[b]	NR
	14	SPMS	29%[e]	7%[c], 29%[b]	NR
	16	PPMS	31%[e]	25%[c], 31%[b]	NR
Gunal et al. [44]	22	RRMS	9%[e]	14%[c], 18%[b]	18%[f]
McDougall and McLeod [45]	63	RRMS 39, SPMS 21 and PPMS 3	3%[d], 3%[g]	0%[c], 16%[b]	45%[f]
Labuz-Roszak and Pierzchala [46]	24	RRMS 11, SPMS 10 and PPMS 3	19%[e]	4%[c], 29%[b]	75%[f]
Lorberboym et al. [47]	10	RRMS 7, SPMS 3	NR	30%[c], 50%[b]	NR
Saari et al. [48]	27	RRMS 21, SPMS 6	NR	NR	52%[f]
Hale et al. [49]	31	RRMS 22, SPMS 5 and PPMS 2 (2 unknown type)	26%[g]	6%[c], 10%[b]	NR
Aghamollaii et al. [50]	30	CIS 9, RRMS 21	NR	NR	77%[f]
Adamec et al. [51]	112	RRMS	11%[g]	NR	NR
Crnošija et al. [52]	24	CIS	38%[d], 8%[g]	4%[c], 0%[b]	31%[i] (out of 16 patients)
Habek et al. [14]	104	CIS	34%[d], 8%[g]	1%[c], 4%[b]	33%[i]
Adamec et al. [15]	40	RRMS	36%[j]	3%[k]	35%[i]
	30	PMS	61%[j]	20%[k]	73%[i]

NR not reported, *CIS* clinically isolated syndrome, *RRMS* relapsing–remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *PMS* progressive multiple sclerosis

[a]Thermoregulatory sweat testing

[b]Deep breathing test

[c]Valsalva ratio

[d]Systolic BP response to Valsalva maneuver

[e]Active standing

[f]Sympathetic skin response

[g]Tilt-table test

[h]Composite measure of three parasympathetic tests including deep breathing and Valsalva ratio

[i]QSART

[j]Adrenergic index

[k]Cardiovagal index

The third aspect of the CASS is sudomotor testing. Traditional neurophysiological measurements of sudomotor function include thermoregulatory sweat testing, QSART, silicone impressions and sympathetic skin response (SSR) [18]. Sweating dysfunction is common in MS, particularly in an advanced disease course. The most frequently used test for evaluating sudomotor function in pwMS is SSR, and it has shown sudomotor abnormalities in 18–94% of pwMS (Table 1). However, this methodology is only a surrogate measure of sudomotor function; it shows high variability within and between subjects and may not be evident in many subjects older than 50 years [18]. QSART, on the other hand, is used to evaluate postganglionic sympathetic cholinergic sudomotor function by measuring the axon-reflex-mediated sweat response, and for this reason it has rarely been studied in pwMS. However, with increased duration of the preganglionic lesion, the response on QSART may become abnormal as well. This was demonstrated in a study investigating cholinergic sweating responses with pilocarpine iontophoresis in pwMS, which showed diminished peripheral sweating responses as a consequence of impaired central autonomic control of sudomotor function [19]. This indicates that QSART may be used for detecting sudomotor dysfunction in MS as well. In line with this, we have shown QSART abnormalities in 33% of pwCIS, 35.0% of pwRRMS and 73.3% of pwPMS [14, 15]. The sudomotor index correlated with both disease duration and EDSS in all patients, and pwPMS had significantly worse QSART results on all tested areas compared to pwRRMS [15]. Whether QSART abnormalities can be used as markers of disease progression remains to be elucidated.

In Fig. 1, four main questions arising from these studies are depicted: (1) Can AD be related to demyelinating lesions on the MRI? (2) What happens with AD with the progression of MS? (3) How is AD related to MS disease course? (4) Is AD related to MS comorbidities?

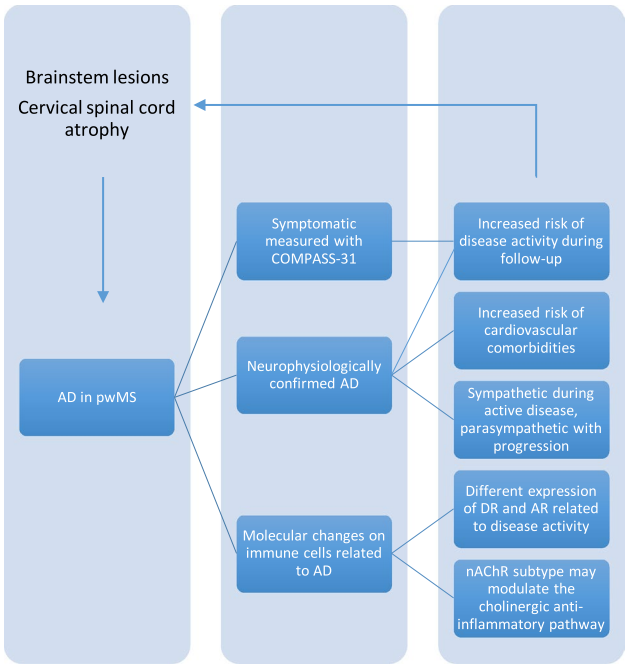

Fig. 1 Autonomic dysfunction (AD) in people with multiple sclerosis (pwMS) can be demonstrated clinically and on a molecular level. Clinically, it can be demonstrated by measuring autonomic symptoms with the Composite Autonomic Symptom Score (COMPASS-31) and neurophysiologically with different autonomic nervous system tests. Both symptomatic and objectively determined AD can be associated with increased risk of multiple sclerosis (MS) disease activity, and abnormalities on different autonomic nervous system tests may indicate an increased risk of cardiovascular comorbidities. The cause of AD in pwMS is probably related to demyelinating lesions in the brainstem and atrophy of the cervical spinal cord; however, once present, it can trigger a vicious circle of new lesion formation, which in turn can worsen AD. Further supporting these clinical observations are molecular changes in immune cells. Changes in the sympathetic autonomic system such as different expression of dopaminergic receptor (DR) D_3 and α_{2A}-adrenergic receptor (AR) mRNAs in peripheral blood mononuclear cells, and dopaminergic receptor D_5 mRNA in T regulatory cells, may be associated with MS disease activity. Similarly, modulation of the cholinergic anti-inflammatory pathway over different subunits of the nicotinic acetylcholine receptor (nAChR) in the peripheral immune system may mediate different effects on MS disease activity

Can AD be related to demyelinating lesions on MRI?

As MRI is the most widely used test in the diagnosis and follow-up of pwMS, several studies have tried to correlate AD with the presence of demyelinating lesions in different brain or spinal cord regions. Only a few studies have found a correlation between ANS dysfunction and brainstem lesions on MRI, two of which found a correlation between sympathetic cardiovascular dysfunction and brainstem lesions [14, 17, 20]. On the other hand, one study showed that ANS dysfunction correlated with spinal cord atrophy, suggesting that AD is secondary to axonal loss rather than to demyelination [11]. Although these results are not robust, they are not surprising, as the brainstem and spinal cord are both areas of the central nervous system responsible for AD. Studies in larger, well-defined cohorts of pwMS using newer MRI techniques might provide more evidence supporting this association.

What happens with AD with the progression of MS?

Only three studies thus far have investigated longitudinal evolution of cardiovascular AD in pwMS [21–23]. The first study addressing this question enrolled people with advanced RRMS and secondary progressive MS (SPMS) with disease duration from 2 to 32 years. The authors only looked at parasympathetic cardiovascular autonomic function over a 1-year period, and found progression in two tests

measuring parasympathetic function (maximum change in heart rate after standing up and the max/min ratio after standing up) [21]. Another study used similar tests but included people with active RRMS with disease duration ranging from 2 to 13 years and follow-up of 2 years, and found progression of parasympathetic AD [22]. In the third and final study longitudinally investigating cardiovascular autonomic function in pwMS, the authors enrolled people with active and stable MS with an average disease duration of 5.5 and 9.3 years, respectively, and used tests of parasympathetic and adrenergic sympathetic function [23]. During a 2-year follow-up, only the test results for parasympathetic function worsened, while there was no change in the results of adrenergic sympathetic function tests. While there is a clear lack of studies with longitudinal evaluation of adrenergic sympathetic function, some hypotheses can be generated from cross-sectional studies evaluating both adrenergic sympathetic and parasympathetic branches in different MS phenotypes (CIS, RRMS and SPMS) which are clearly related to time. It was shown that parasympathetic dysfunction and sympathetic dysfunction were present in 5% in 43% of pwCIS, [14], 2% and 36% of pwRRMS, and 20% and 61% of pwPMS, respectively [15]. If we put these studies into the context of longitudinal studies, there seems to exist a distinct pattern of dysautonomia which depends on different phases of the disease.

How is AD related to MS disease course?

There are several lines of evidence to suggest that interactions between the immune and autonomic systems may alter the disease course of MS [3]. However, data on how these abnormalities influence the evolution of MS over time are sparse. Only two studies have investigated the role of ANS abnormalities in pwCIS. In the first study, the authors investigated whether ANS dysfunction presenting as postural orthostatic tachycardia syndrome (POTS) could predict conversion to MS in pwCIS over a 6-month follow-up. POTS was identified as a significant predictor of early conversion to MS, with an odds ratio of 2.34 [24]. The second study aimed to evaluate the potential role of ANS abnormalities in disease activity (relapses and new MRI lesions) and disease progression in 121 pwCIS over a mean follow-up duration of 2.9 years [25]. The results showed that symptoms of AD measured with COMPASS-31 (COMPASS-31 > 7.32) were associated with a 2.7-fold increased risk of next relapse in pwCIS. These results are of particular interest, because a recent study observed that pwMS had significantly higher risk of presenting up to 10 years prior to a first demyelinating event with gastric, intestinal, urinary and anorectal disturbances, anxiety, depression, insomnia, fatigue, headache and various types of pain [26]. These autonomic symptoms that precede MS for up to 10 years are called MS prodrome, and the risk of MS increases proportionally with the number of symptoms present. If we put the results of the former study into the context of autonomic MS prodrome, we may speculate that ANS is an important predictor of disease activity, even before the first demyelinating event. If these results were to be confirmed in a second independent study, they would be of great importance for early detection of pwMS at risk for higher disease activity.

Is AD related to MS comorbidities?

As discussed previously, one of the most frequent ANS abnormalities in MS is abnormalities of the cardiovascular autonomic system. This might be related to epidemiological studies showing that pwMS may have an increased risk of ischemic heart disease and congestive heart failure when compared with the general population [27], and that pwMS have a markedly increased risk of myocardial infarction in the first year after the MS diagnosis [28]. A recently published retrospective study found that pwMS have adrenergic hyperactivity manifested as an increase in α-adrenergic baroreflex sensitivity (α-BRSa) compared with healthy controls (HC) [29]. In the same study, the authors also observed a positive correlation between α-BRSa and systolic BP in the tilted position. These results are interesting knowing that adrenergic hyperactivity, which is a hallmark of arterial hypertension [30], may contribute to the increased risk of ischemic heart disease and congestive heart failure in pwMS. Further studies are needed to confirm these preliminary results.

ANS–immune system interactions and their role in MS

Interactions between the ANS and the immune system exist on several levels, and are beyond the scope of this review article. Several recent articles have reviewed experimental evidence that the ANS plays a crucial role in the communication between the nervous system and the immune system [53, 54].

Few studies have investigated changes in the interaction between ANS and the immune system in pwMS. In vitro studies have shown that interferon β leads to reduced intracellular and increased extracellular levels of epinephrine, norepinephrine and dopamine [55]. This effect is the result of induction of catecholamine release from the cells to the medium and increased production of all three catecholamines. These results are interesting if we put them into a clinical context, with a study that showed a reduced likelihood of relapse with increasing levels of serum epinephrine [25].

In both RRMS and PPMS, there is an increase in the β2-adrenergic receptor density on mononuclear cells in peripheral blood, which is associated with clinical and radiological disease activity [56, 57]. Furthermore, responsiveness of β2-adrenergic receptors to isoproterenol was shown to be absent in untreated patients and was restored after interferon β treatment [58]. On the other hand, gene expression studies showed that the expression of mRNA for β-adrenergic receptors was reduced in mononuclear cells of peripheral blood from untreated patients with relapsing MS [59]. In untreated pwMS, there is reduced expression and activity of D_1-like dopaminergic receptors and β2-adrenergic receptors on circulating peripheral blood mononuclear cells and on $CD4^+$ T effector lymphocytes and overexpression of D_1-like dopaminergic receptors on $CD4^+$ $CD25^{high}$ T regulatory lymphocytes [60]. The opposite is seen in pwMS treated with interferon β [59, 60]. Furthermore, dopaminergic receptor D_3 and α2A-adrenergic receptor mRNAs in peripheral blood mononuclear cells, and dopaminergic receptor D_5 mRNA in T regulatory cells, may be associated with the risk of conversion to MS in pwCIS within 12 months of clinical presentation [61].

A second branch of the ANS, the parasympathetic nervous system, plays a major role in alerting the central nervous system to the presence of inflammation via inflammatory cytokines [62]. These afferent signals are transmitted by the vagus nerve and trigger an anti-inflammatory response, termed "cholinergic anti-inflammatory pathway", which is postulated to suppress inflammatory and immune responses by integrating signaling in the immune and nervous systems [3, 63]. This efferent part of the cholinergic anti-inflammatory pathway ends in the α-7 subunit of nicotinic acetylcholine receptors, which are expressed in immune cells (T cells, B cells, monocytes and endothelial cells), leading to the release of anti-inflammatory cytokines [63, 64].

Several studies in animal models of MS argue on the relevance of the cholinergic anti-inflammatory pathway in MS pathogenesis. In mice with experimental autoimmune acute encephalomyelitis, deficient in subunit α-7 nicotinic acetylcholine receptors, subtle changes in the expression of pro-inflammatory and anti-inflammatory cytokines were observed, with higher expression of interleukin 10, interleukin 1 factor 9, and inhibin α [65]. More pronounced changes were observed in another study, which demonstrated that subunit α-7 nicotinic acetylcholine receptors play an important role in the reduction of the inflammatory response conferred by nicotine in autoimmune experimental acute encephalomyelitis [66]. However, recent data demonstrate that several nicotinic acetylcholine receptor subtypes are involved, albeit differently, in the cholinergic anti-inflammatory pathway, indicating that each nicotinic acetylcholine receptor subtype may modulate unique cellular immune functions [67]. Specifically, it has been suggested that disease exacerbation (or even induction) is mediated at least in part via α-9 nicotinic acetylcholine receptors in peripheral immune cells, but a protective role for central nervous system α-7 nicotinic acetylcholine receptors has also been suggested [68]. The discovery of acetylcholine-producing T cells capable of regulating inflammation has proved the importance of neural circuits as a rheostat mechanism in immunomodulation [69].

As nicotine, which acts via nicotinic acetylcholine receptors, is one of the principal components of cigarette smoke, it is interesting that a substantial body of evidence supports the causal involvement of smoking in the development and progression of MS [70]. Studies on the effects of nicotine on the immune system have been contradictory, with some finding pro- and some anti-inflammatory effects [71]. Studies in an animal model of MS, experimental autoimmune encephalomyelitis (EAE), found that nicotine improved EAE symptoms, clinical scores and demyelination status, in contrast to cigarette smoke condensate, which caused a worsening of the disease course [72]. Even more interesting, a therapeutic intervention in EAE combining mesenchymal stem cells and nicotine led to a significant reduction in cumulative disease disability that was superior to treatment with either therapy alone [73]. Furthermore, the combination treatment caused a significant decline in the production of the pro-inflammatory interleukin 17, tumor necrosis factor-α, and interferon-γ cytokines, and simultaneously caused a meaningful increase in the production of the anti-inflammatory interleukin 10.

All these data provide a molecular framework for previously mentioned clinical and neurophysiological data supporting the role of ANS dysfunction in MS. However, correlation studies taking into account clinical, neurophysiological and molecular aspects are lacking, and would help us gain a better understanding of immune–ANS interaction disturbances in MS.

Conclusion

The results of the studies published thus far have shown a distinctive pattern of AD in pwMS. While disease activity, which is more prevalent in pwCIS and early RRMS, is associated with sympathetic nervous system dysfunction, parasympathetic nervous system dysfunction becomes more evident with the progression of the disease, with the highest percentages of involvement seen in advanced progressive MS. On a molecular level, changes in the expression of different receptors responsible for the communication between the ANS and immune system may modulate inflammatory response and thus may influence MS disease activity or progression. Whether these observed ANS changes are drivers of the inflammation and/or neurodegeneration, or are just a

consequence of MS lesions in the central nervous system, remains to be elucidated.

Author contributions MH: Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and administrative, technical, and material support.

Funding None received for the preparation of this manuscript.

Compliance with ethical standards

Conflict of interest The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, and royalties. No writing assistance was utilized in the production of this manuscript.

References

1. Wu GF, Alvarez E (2011) The immuno-pathophysiology of multiple sclerosis. Neurol Clin 29:257–278
2. Adamec I, Habek M (2013) Autonomic dysfunction in multiple sclerosis. Clin Neurol Neurosurg 115(Suppl 1):S73–S78
3. Racosta JM, Kimpinski K (2016) Autonomic dysfunction, immune regulation, and multiple sclerosis. Clin Auton Res 26:23–31
4. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA (1999) The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology 52:523–528
5. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W (2012) COMPASS 31: a refined and abbreviated composite autonomic symptom score. Mayo Clin Proc 87:1196–1201
6. Drulović J, Gavrilović A, Crnošija L, Kisić-Tepavčević D, Krbot Skorić M, Ivanović J, Adamec I, Dujmović I, Junaković A, Marić G, Martinović V, Pekmezović T, Habek M (2017) Validation and cross-cultural adaptation of the COMPASS-31 in croatian and serbian patients with multiple sclerosis. Croat Med J 58:342–348
7. Vieira B, Costa A, Videira G, Sá MJ, Abreu P (2015) Prevalence of autonomic dysfunction in patients with multiple sclerosis. Acta Med Port 28:51–55
8. Cortez MM, Nagi Reddy SK, Goodman B, Carter JL, Wingerchuk DM (2015) Autonomic symptom burden is associated with MS-related fatigue and quality of life. Mult Scler Relat Disord 4:258–263
9. Ruška B, Pavičić T, Pavlović I, Junaković A, Adamec I, Crnošija L, Krbot Skorić M, Habek M (2018) Performance of the COMPASS-31 questionnaire with regard to autonomic nervous system testing results and medication use: a prospective study in a real-life setting. Neurol Sci 39:2079–2084
10. Acevedo AR, Nava C, Arriada N, Violante A, Corona T (2000) Cardiovascular dysfunction in multiple sclerosis. Acta Neurol Scand 101:85–88
11. de Seze J, Stojkovic T, Gauvrit JY, Devos D, Ayachi M, Cassim F, Saint Michel T, Pruvo JP, Guieu JD, Vermersch P (2001) Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. J Neurol 248:297–303
12. Flachenecker P, Wolf A, Krauser M, Hartung HP, Reiners K (1999) Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. J Neurol 246:578–586
13. Low PA (1993) Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 68:748–752
14. Habek M, Crnošija L, Lovrić M, Junaković A, Krbot Skorić M, Adamec I (2016) Sympathetic cardiovascular and sudomotor functions are frequently affected in early multiple sclerosis. Clin Auton Res 26:385–393
15. Adamec I, Crnošija L, Junaković A, Krbot Skorić M, Habek M (2018) Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype. Clin Neurophysiol 129:1588–1594
16. Arbogast SD, Alshekhlee A, Hussain Z, McNeeley K, Chelimsky TC (2009) Hypotension unawareness in profound orthostatic hypotension. Am J Med 122:574–580
17. Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C (1993) Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. J Neurol Sci 120:82–86
18. Illigens BM, Gibbons CH (2009) Sweat testing to evaluate autonomic function. Clin Auton Res 19:79–87
19. Davis SL, Wilson TE, Vener JM, Crandall CG, Petajan JH, White AT (1985) Pilocarpine-induced sweat gland function in individuals with multiple sclerosis. J Appl Physiol 2005(98):1740–1744
20. Saari A, Tolonen U, Pääkkö E, Suominen K, Pyhtinen J, Sotaniemi K, Myllylä V (2004) Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. Clin Neurophysiol 115:1473–1478
21. Nasseri K, TenVoorde BJ, Adèr HJ, Uitdehaag BM, Polman CH (1998) Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. J Neurol Sci 155:50–54
22. Nasseri K, Uitdehaag BM, van Walderveen MA, Ader HJ, Polman CH (1999) Cardiovascular autonomic function in patients with relapsing remitting multiple sclerosis: a new surrogate marker of disease evolution? Eur J Neurol 6:29–33
23. Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV (2001) Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult Scler 7:327–334
24. Habek M, Krbot Skorić M, Crnošija L, Gabelić T, Barun B, Adamec I (2017) Postural orthostatic tachycardia predicts early conversion to multiple sclerosis after clinically isolated syndrome. Eur Neurol 77:253–257
25. Krbot Skorić M, Crnošija L, Gabelić T, Barun B, Adamec I, Junaković A, Pavičić T, Ruška B, Habek M (2019) Autonomic symptom burden can predict disease activity in early multiple sclerosis. Mult Scler Relat Disord 28:250–255
26. Disanto G, Zecca C, MacLachlan S, Sacco R, Handunnetthi L, Meier UC, Simpson A, McDonald L, Rossi A, Benkert P, Kuhle J, Ramagopalan SV, Gobbi C (2018) Prodromal symptoms of multiple sclerosis in primary care. Ann Neurol 83:1162–1173
27. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Cutter G, Reingold S, Sorensen PS (2015) A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult Scler 21:318–331
28. Christiansen CF, Christensen S, Farkas DK, Miret M, Sørensen HT, Pedersen L (2010) Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 35:267–274
29. Habek M, Mutak T, Nevajdić B, Pucić D, Crnošija L, Krbot Skorić M (2018) Adrenergic hyperactivity: a missing link between multiple sclerosis and cardiovascular comorbidities? Acta Neurol Belg. https://doi.org/10.1007/s13760-018-1051-4
30. Grassi G, Seravalle G, Brambilla G, Pini C, Alimento M, Facchetti R, Spaziani D, Cuspidi C, Mancia G (2014) Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. Int J Cardiol 177:1020–1025

31. Noronha MJ, Vas CJ, Aziz H (1968) Autonomic dysfunction (sweating responses) in multiple sclerosis. J Neurol Neurosurg Psychiatry 31:19–22
32. Mutani R, Clemente S, Lamberti A, Monaco F (1982) Assessment of autonomic disturbances in multiple sclerosis by measurement of heart rate responses to deep breathing and to standing. Ital J Neurol Sci 3:111–114
33. Senaratne MP, Carroll D, Warren KG, Kappagoda T (1984) Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry 47:947–952
34. Pentland B, Ewing DJ (1987) Cardiovascular reflexes in multiple sclerosis. Eur Neurol 26:46–50
35. Yokota T, Matsunaga T, Okiyama R, Hirose K, Tanabe H, Furukawa T, Tsukagoshi H (1991) Sympathetic skin response in patients with multiple sclerosis compared with patients with spinal cord transection and normal controls. Brain 114:1381–1394
36. Anema JR, Heijenbrok MW, Faes TJ, Heimans JJ, Lanting P, Polman CH (1991) Cardiovascular autonomic function in multiple sclerosis. J Neurol Sci 104:129–134
37. Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ (1993) Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. J Neurol 240:139–143
38. Gutrecht JA, Suarez GA, Denny BE (1993) Sympathetic skin response in multiple sclerosis. J Neurol Sci 118:88–91
39. Elie B, Louboutin JP (1995) Sympathetic skin response (SSR) is abnormal in multiple sclerosis. Muscle Nerve 18(2):185–189
40. Linden D, Diehl RR, Berlit P (1995) Subclinical autonomic disturbances in multiple sclerosis. J Neurol 242:374–378
41. Caminero AB, Pérez-Jiménez A, Barreiro P, Ferrer T (1995) Sympathetic skin response: correlation with autonomic and somatic involvement in multiple sclerosis. Electromyogr Clin Neurophysiol 35:457–462
42. Linden D, Diehl RR, Kretzschmar A, Berlit P (1997) Autonomic evaluation by means of standard tests and power spectral analysis in multiple sclerosis. Muscle Nerve 20:809–814
43. Merkelbach S, Dillmann U, Kölmel C, Holz I, Muller M (2001) Cardiovascular autonomic dysregulation and fatigue in multiple sclerosis. Mult Scler 7:320–326
44. Gunal DI, Afsar N, Tanridag T, Aktan S (2002) Autonomic dysfunction in multiple sclerosis: correlation with disease-related parameters. Eur Neurol 48:1–5
45. McDougall AJ, McLeod JG (2003) Autonomic nervous system function in multiple sclerosis. J Neurol Sci 215(1–2):79–85
46. Labuz-Roszak B, Pierzchala K (2007) Difficulties in the diagnosis of autonomic dysfunction in multiple sclerosis. Clin Auton Res 17:375–377
47. Lorberboym M, Lampl Y, Nikolov G, Sadeh M, Gilad R (2008) I-123 MIBG cardiac scintigraphy and autonomic test evaluation in multiple sclerosis patients. J Neurol 255:211–216
48. Saari A, Tolonen U, Pääkkö E, Suominen K, Pyhtinen J, Sotaniemi KA, Jauhiainen J, Myllylä VV (2008) Sympathetic skin responses in multiple sclerosis. Acta Neurol Scand 118:226–231
49. Hale LA, Nukada H, Du Plessis LJ, Peebles KC (2009) Clinical screening of autonomic dysfunction in multiple sclerosis. Physiother Res Int 14:42–55
50. Aghamollaii V, Harirchian MH, Modabbernia A, Ghaffarpour M, Mousavi M, Tafakhori A (2011) Sympathetic skin response (SSR) in multiple sclerosis and clinically isolated syndrome: a case-control study. Neurophysiol Clin 41:161–171
51. Adamec I, Bach I, Barušić AK, Mišmaš A, Habek M (2013) Assessment of prevalence and pathological response to orthostatic provocation in patients with multiple sclerosis. J Neurol Sci 324:80–83
52. Crnošija L, Adamec I, Lovrić M, Junaković A, Krbot Skorić M, Lušić I, Habek M (2016) Autonomic dysfunction in clinically isolated syndrome suggestive of multiple sclerosis. Clin Neurophysiol 127:864–869
53. Benarroch EE (2019) Autonomic nervous system and neuroimmune interactions: new insights and clinical implications. Neurology. https://doi.org/10.1212/wnl.0000000000006942
54. Sternberg EM (2006) Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol 6:318–328
55. Cosentino M, Zaffaroni M, Ferrari M, Marino F, Bombelli R, Rasini E, Frigo G, Ghezzi A, Comi G, Lecchini S (2005) Interferon-gamma and interferon-beta affect endogenous catecholamines in human peripheral blood mononuclear cells: implications for multiple sclerosis. J Neuroimmunol 162:112–121
56. Karaszewski JW, Reder AT, Anlar B, Arnason GW (1993) Increased high affinity beta-adrenergic receptor densities and cyclic AMP responses of CD8 cells in multiple sclerosis. J Neuroimmunol 43:1–7
57. Zoukos Y, Thomaides TN, Kidd D, Cuzner ML, Thompson A (2003) Expression of beta 2 adrenoreceptors on peripheral blood mononuclear cells in patients with primary and secondary progressive multiple sclerosis: a longitudinal 6 month study. J Neurol Neurosurg Psychiatry 74:197–202
58. Giorelli M, Livrea P, Trojano M (2004) Post-receptorial mechanisms underlie functional disregulation of beta2-adrenergic receptors in lymphocytes from multiple sclerosis patients. J Neuroimmunol 155:143–149
59. Zaffaroni M, Marino F, Bombelli R, Rasini E, Monti M, Ferrari M, Ghezzi A, Comi G, Lecchini S, Cosentino M (2008) Therapy with interferon-beta modulates endogenous catecholamines in lymphocytes of patients with multiple sclerosis. Exp Neurol 214:315–321
60. Marino F, Cosentino M (2013) Adrenergic modulation of immune cells: an update. Amino Acids 45:55–71
61. Cosentino M, Zaffaroni M, Legnaro M, Bombelli R, Schembri L, Baroncini D, Bianchi A, Clerici R, Guidotti M, Banfi P, Bono G, Marino F (2016) Dopaminergic receptors and adrenoceptors in circulating lymphocytes as putative biomarkers for the early onset and progression of multiple sclerosis. J Neuroimmunol 298:82–89
62. Bianchi ME (2007) DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 81:1–5
63. Tracey KJ (2009) Reflex control of immunity. Nat Rev Immunol 9:418–428
64. De Jonge WJ, Ulloa L (2007) The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. Br J Pharmacol 151:915–929
65. Nicolussi EM, Huck S, Lassmann H, Bradl M (2009) The cholinergic anti-inflammatory system limits T cell infiltration into the neurodegenerative CNS, but cannot counteract complex CNS inflammation. Neurobiol Dis 35:24–31
66. Hao J, Simard AR, Turner GH et al (2011) Attenuation of CNS inflammatory responses by nicotine involves α7 and non-α7 nicotinic receptors. Exp Neurol 227:110–119
67. Simard AR, Gan Y, St-Pierre S, Kousari A, Patel V, Whiteaker P, Morley BJ, Lukas RJ, Shi FD (2013) Differential modulation of EAE by α9*- and β2*-nicotinic acetylcholine receptors. Immunol Cell Biol 91:195–200
68. Liu Q, Whiteaker P, Morley BJ, Shi FD, Lukas RJ (2017) Distinctive Roles for α7*- and α9*-Nicotinic acetylcholine receptors in inflammatory and autoimmune responses in the murine experimental autoimmune encephalomyelitis model of multiple sclerosis. Front Cell Neurosci 11:287
69. Rosas-Ballina M, Olofsson PS, Ochani M et al (2011) Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science 334:98–101

70. Degelman ML, Herman KM (2017) Smoking and multiple sclerosis: a systematic review and meta-analysis using the Bradford Hill criteria for causation. Mult Scler Relat Disord 17:207–216
71. Gomes JP, Watad A, Shoenfeld Y (2018) Nicotine and autoimmunity: the lotus' flower in tobacco. Pharmacol Res 128:101–109
72. Gao Z, Nissen JC, Ji K, Tsirka SE (2014) The experimental autoimmune encephalomyelitis disease course is modulated by nicotine and other cigarette smoke components. PLoS One 9:e107979
73. Khezri S, Abtahi Froushani SM, Shahmoradi M (2018) Nicotine augments the beneficial effects of mesenchymal stem cell-based therapy in rat model of multiple sclerosis. Immunol Invest 47(2):113–124