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REVIEW

Cardiovascular autonomic dysfunction in multiple sclerosis: A meta-analysis

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Multiple sclerosis;
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Abstract
Background and objective: The definition of cardiovascular autonomic dysfunction in patients with multiple sclerosis is controversial. Thus, its true prevalence is unknown. We performed a systematic review and meta-analysis to compare the proportion of patients with multiple sclerosis that would be diagnosed with cardiovascular dysautonomia using a definition of at least one abnormal cardiac autonomic test vs. at least two abnormal studies.
Methods: We searched PubMed, Embase, and Scopus from 1980 to December 2013 for publications reporting abnormal autonomic tests in patients with multiple sclerosis. We performed random-effects meta-analyses for calculating the proportion of patients diagnosed with autonomic dysfunction with both definitions.
Results: We included 16 studies comprising 611 patients with multiple sclerosis, assessing ≥ 3 cardiovascular autonomic tests. The proportion of patients with autonomic dysfunction was two-fold higher ($p=0.006$) when using the definition of only one abnormal autonomic test (42.1%) compared to that using at least two abnormal results (18.8%).
Conclusions: We found a wide variation in the proportion of patients with multiple sclerosis diagnosed with cardiovascular dysautonomia by using the two definitions. Consensus is needed to define autonomic dysfunction in patients with multiple sclerosis. In the meantime, we encourage investigators to report results using both thresholds.

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Contents

1. Introduction

The interactions between autonomic dysfunction and the immune system, as well as the role of autonomic dysfunction in the pathogenesis and progression of multiple sclerosis, have been a matter of increasing interest (Cosentino and Marino, 2013). Several studies attempted to relate autonomic dysfunction of patients with multiple sclerosis to demyelinating lesions within specific regions of the central nervous system (Acevedo et al., 2000). However these data are inconclusive and the nature of the pathophysiological association between autonomic dysfunction and multiple sclerosis remains unclear (Flachenecker, 2007). Identifying autonomic dysfunction in patients with multiple sclerosis is relevant both from the clinical (i.e. diagnosis and treatment) and research (i.e. identifying potential treatment targets) perspectives (Racosta and Kremenchutzky, 2014). Several types of autonomic dysfunction have been described among multiple sclerosis(MS) patients, comprising cardiovascular (Adamec and Habek, 2013), bladder, sexual (Schairer et al., 2014), and gastrointestinal involvement (el-Maghraby et al., 2005), as well as impairment of thermoregulation (Ueno et al., 2000) and pupillary dysfunction (de Seze et al., 2001). As cardiovascular autonomic dysfunction has been correlated with landmark pathophysiological processes of MS (e.g. underlying inflammation and neurodegeneration), identifying this type of autonomic dysfunction may be of critical importance (Nasseri et al., 1999; Kodounis et al., 2005; Lorberboym et al., 2008; Vita et al., 1993).

One of the issues when reviewing literature on the MS population with cardiovascular autonomic dysfunction is that the definition varies across studies and to date there is no consensus on the diagnostic criteria (Nasseri et al., 1999; Kodounis et al., 2005; Lorberboym et al., 2008; Vita et al., 1993; Anema et al., 1991; McDougall and McLeod, 2003; Ferini-Strambi et al., 1995; Frontoni et al., 1996; Flachenecker et al., 1999; Acevedo et al., 2000; Merkelbach et al., 2001; Gunal et al., 2002; Labuz-Roszak and Pierzchala 2007; Hale et al., 2009; Amarenco et al., 2013). Many studies report the number of abnormal autonomic tests (Nasseri et al., 1999; Kodounis et al., 2005; Lorberboym et al., 2008; Anema et al., 1991), while others define dysautonomia as at least 2 abnormal tests (Vita et al., 1993; McDougall and McLeod 2003; Ferini-Strambi et al., 1995; Frontoni et al., 1996; Flachenecker et al., 1999; Acevedo et al., 2000; Merkelbach et al., 2001; Gunal et al., 2002; Labuz-Roszak and Pierzchala 2007; Hale et al., 2009; Amarenco et al., 2013).

Based on studies of patients with chronic renal failure, Vita et al. suggested that cardiovascular autonomic dysfunction should be diagnosed in the presence of at least 2 abnormal autonomic tests (Vita et al., 1991). In contrast,

Table 1 Search strategy and results.

Search term	Number of articles
PubMed	**1854**
Multiple Sclerosis[Mesh]) and "Autonomic Nervous System"[Mesh]	167
Multiple Sclerosis[Mesh]) and "Autonomic Nervous System Diseases" [Mesh]	108
Multiple Sclerosis[Mesh]) and "Cardiovascular System" [Mesh]	1118
Multiple Sclerosis[Mesh]) and "Sympathetic Nervous System" [Mesh]	47
Multiple Sclerosis[Mesh]) and "Parasympathetic Nervous System" [Mesh]	64
Multiple Sclerosis[Mesh and hearth rate variability	15
Multiple Sclerosis[Mesh] and autonomic tests	56
Multiple Sclerosis[Mesh] and autonomic dysfunction	201
Multiple Sclerosis[Mesh] and cardiovascular autonomic dysfunction	56
Multiple Sclerosis[Mesh] and sympathetic skin response	22
EMBASE	**983**
Multiple Sclerosis and "Autonomic Nervous System"	196
Multiple Sclerosis and "Autonomic Dysfunction"	143
Multiple Sclerosis and "Cardiovascular System"	96
Multiple Sclerosis and "Sympathetic"	245
Multiple Sclerosis and "Parasympathetic"	61
Multiple Sclerosis and Hearth Rate	242
Scopus	**288**
Multiple Sclerosis and Autonomic Dysfunction	288
Total	**3125**