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The Diagnostic Journey of Dysautonomia Patients: Insights from a Patient-Reported Outcome Study

John A. O'Dell, MSN, MBA[1], Ash Walker, DHSc[2], Andrew J. Latham, PhD[3], Daniel J. Parisian, PhD[4], Lindsay E. Branch, BS[1], Dreena D. Vanderburg[1], Ava A. Cox[1], Shelley Chavis[1], and Silvia E. Smith, PhD[1,5]

Abstract

Dysautonomia refers to any disorder involving altered function of the autonomic nervous system. Dysautonomia can be debilitating as it often affects multiple organ systems. The diagnostic journey for individuals affected by dysautonomia can be hindered by symptom overlap with other conditions and by limited access to autonomic specialists. The present patient-reported outcome study aims to characterize the diagnostic journey of 672 adult individuals affected by different types of dysautonomia. The average time to diagnosis was 7.7 years (SD 10 years) and diagnosis was made primarily by cardiologists, followed by neurologists, and internists or primary care physicians. Common comorbid conditions are Ehlers-Danlos syndrome, mast cell disorders, vitamin deficiency, fibromyalgia, and myalgic encephalomyelitis, all of which can contribute to the symptoms burden and can potentially confound the diagnostic process. We suggest that the prolonged time to diagnosis contributes to morbidity and compounds the psychological and economic burden of dysautonomia. Raising awareness about the numerous obstacles that hinder the diagnostic process among both clinicians and dysautonomia patients is the first step to reduce morbidity and improve clinical outcomes.

Keywords

Dysautonomia, diagnosis, patient journey, comorbid conditions

Introduction

Dysautonomia: Classification, Etiology, and Symptoms

The autonomic nervous system (ANS) regulates involuntary physiological processes such as respiration, blood pressure, heart rate, pupillary dilation, sweating, digestion, and sexual arousal.[1] Autonomic disorders (ie, dysautonomia) are clinically classified as orthostatic intolerance syndromes, central dysautonomia, and small fiber neuropathies. Briefly, orthostatic intolerance is characterized by the presence of symptoms which occur while standing or with prolonged sitting and that resolve with recumbence. The most common orthostatic syndrome is postural orthostatic tachycardia syndrome (POTS), which is also a feature of long COVID,[2] may result from virus- or immune-mediated disruption of the autonomic nervous system.[3] Central dysautonomia results from neurodegenerative, autoimmune, and vascular disease, as well as trauma to the central nervous system. Finally, small fiber neuropathies can affect different types of small nerve fibers, including both sensory and autonomic fibers, and can be classified as 1) primary; 2) secondary, if the etiology is related to systemic autoimmunity or inflammatory processes, environmental exposure, or

[1] Department of Biology, University of North Carolina Pembroke, Pembroke, NC, USA
[2] Department of Kinesiology, University of North Carolina Pembroke, Pembroke, NC, USA
[3] Department of Mathematics and Computer Science, University of North Carolina Pembroke, Pembroke, NC, USA
[4] Department of Economics, Marketing, Entrepreneurship, and Analytics, University of North Carolina Pembroke, Pembroke, NC, USA
[5] Department of Internal Medicine, Pulmonary Division, University of Utah School of Medicine, Salt Lake City, UT, USA

Corresponding Author:
Silvia E. Smith, Department of Biology, University of North Carolina Pembroke, P.O. Box 1510, Pembroke, NC 28372, USA.
Email: silvia.smith@uncp.edu

diabetes; or 3) idiopathic, if the etiology is unknown.[4,5] Autonomic symptoms vary depending on the etiology and can be broadly categorized as orthostatic (eg, lightheadedness, palpitations, dyspnea, exercise intolerance, nausea, and vertigo), non-orthostatic (eg, dry eyes/mouth, diarrhea/constipation, and cold/heat intolerance), or diffused (eg, fatigue, sleep disturbances, and cognitive dysfunction), with some patients often experiencing a combination of symptoms.[4,6] Thus, due to multi-system involvement, the impact of dysautonomia-related symptoms can profoundly affect dysautonomia patients, including their ability to work full time.[7]

Barriers to a Prompt Diagnosis

In most cases, a clinician can assess autonomic nervous system function with a brief physical examination and a targeted medical history; however, once dysautonomia is suspected, advanced testing may be necessary to identify the type of autonomic disorder and determine the best clinical management.[8] Access to specialized testing centers can be hindered by several factors, including geographical and financial barriers, insurance coverage, or prolonged wait times; these variables can protract the diagnostic period and the symptom burden for the patient. Several studies have reported different averaged timeframes from symptom onset to diagnosis for POTS patients: 6.4–7.7 years in a cohort of 42 individuals,[9] 5.9 years in a cohort of 696 individuals,[10] approximately 2 years in a large cohort of 4835 individuals,[11] and more than 2 years in a pediatric POTS population of 708 individuals.[6] The diagnostic delay stems from a variety of factors, including the attribution of symptoms to psychogenic etiology, clinician dismissiveness,[11-13] and limited access to specialized medical centers.[5] Dysautonomia International reported that 50% of individuals affected by POTS (n = 342) traveled more than 100 miles to receive healthcare, and 27% of patients saw 10 or more physicians before receiving a formal diagnosis, with 8% seeing more than 20 physicians.[10] The diagnostic delay negatively affects dysautonomia patients as visits to multiple physicians are financially burdensome and emotionally distressing.[12]

Characterization of the Diagnostic Journey of Dysautonomia Patients

Dysautonomia awareness has grown since the COVID-19 epidemic, which has caused a rapid increase in autonomic disorders associated with long-COVID-19. Historically, the diagnostic journey of people affected by dysautonomia has been difficult, and it required assessment by multiple physicians, especially those who practiced at large specialized medical centers.[9] To characterize the diagnostic journey of dysautonomia patients, using health-related information reported directly from the patient, the present study aims to 1) compute the average time from symptom onset to diagnosis in a dysautonomia cohort comprising different types of autonomic disorders, 2) determine which types of clinicians most frequently diagnose the autonomic disorder, 3) identify the type of clinical setting in which the diagnosis is made (ie, medical research centers vs community clinics), and 4) determine which comorbid conditions are prevalent in this cohort. The overarching goal of this project is to raise awareness about the logistical, financial, and clinical challenges that dysautonomia patients face as part of their diagnostic journey.

Methods

The dysautonomia umbrella includes several disorders, with POTS being the most common and the focus of several cross-sectional or cohort studies.[6,12,14,15] However, to our knowledge, this is the first study to enroll individuals affected by any autonomic disorder. We enrolled 672 willing participants in collaboration with nine nonprofit dysautonomia organizations, which advertised for the study on their social media pages. Participants met the following inclusion criteria: 1) age 18 years or older at the time of consent, 2) formal diagnosis of any type of ANS dysfunction, 3) able to read and write English, and 4) autonomously consent to participate in a research study. As this is a no greater than minimal risk study, participants who passed the screening questionnaire self-consented by reading and electronically signing the informed consent form. Data from all instruments were collected and managed using REDCap electronic data capture tools.[16] After completing the informed process, participants provided basic demographic information and completed the 'Dysautonomia Diagnosis and Comorbid Conditions' instrument. We designed this instrument to allow participants to easily identify formal diagnoses made by clinicians using branching logic to facilitate completion (Appendix 1).

Dysautonomia is often comorbid with other disorders. Recognition of concomitant conditions can impact the diagnostic journey of dysautonomia patients by raising suspicion for underlying autonomic dysfunction. To capture the prevalence of comorbid conditions in our cohort, we provided a list of the most common comorbid conditions typically associated with autonomic dysfunction,[4,8,12,17-20] with the option of including disorders not listed. Dysautonomia can occur as part of systemic autoimmune disorders or as direct autoimmunity against the nervous system.[2,21-24] Because specific autoantibodies are not systematically assayed, especially outside of large medical centers, we asked participants to differentiate only between two broad categories: 1) dysautonomia secondary to a rheumatological condition (eg, Sjögren's syndrome) and 2) other autoimmune-mediated form of dysautonomia. Moreover, we characterized the participants' diagnostic journey by asking about the number of years from symptom onset to diagnosis, the medical specialty of the clinician(s) who made the diagnosis, and whether the diagnosis was made at a large medical center or at a

smaller clinic, since access to testing equipment and subspecialized clinicians varies.

Results

Cohort Demographic Structure

The aim of this project is to characterize the diagnostic journey of individuals affected by any form of dysautonomia using patient-reported data. As shown in Table 1, the cohort is composed mostly of females (90.4%), with males and non-binary individuals representing the minority. Some participants preferred not to report their gender. The ethnic composition of the cohort consists primarily of non-Hispanic or non-Latino individuals (90.6%), with a small percentage of individuals choosing not to report ethnicity. We offered participants the ability to self-identify with several racial categories, including American Indian/Alaskan Native, Asian, African, Caucasian/European, more than one race, and unknown/not reported (Table 1). The overrepresentation of females of European descent in the cohort is consistent with previous studies[8,25,26] and may reflect the epidemiology of dysautonomia, not necessarily the propensity of these demographic groups to enroll in research studies. The average age of the study participants is 41.79 years (SD 12.95 years), with a median age of 41 years. While dysautonomia, and especially POTS, primarily affects females of child-bearing age,[25,27,28] our study excluded participants younger than 18 years of age.

Timing and Clinical Setting of Diagnosis

Ideally, the diagnostic journey is a collaborative patient-centered process through which clinicians gather and evaluate information to make a diagnosis.[29] Given the complexity and multi-organ involvement of autonomic symptoms, different specialists may be involved in the diagnostic process, possibly lengthening the time to diagnosis. Nearly half of the participants reported that the diagnosis was made at an academic medical center, although 10% of participants did not know whether the diagnosing clinician was affiliated with an academic center. Table 2 shows that 53% of participants reported that the diagnosis was made by a cardiologist, followed by a neurologist (26.5%), an internist (6.1%), and a family medical practitioner (4.7%). This is likely a reflection of the predominance of cardiopulmonary symptoms associated with autonomic dysfunction. On average, the length of time from the onset of symptoms to diagnosis in this cohort is 7.7 years (SD 10 years), which is slightly higher than previously reported estimates of 2–6 years.[5,8,30] The COVID-19 pandemic contributed to an increase in post-viral dysautonomia cases,[31-33] likely lengthening the wait times for autonomic and invasive cardiopulmonary exercise testing often used to evaluate autonomic function.

Table 1. Cohort Demographics.

Demographics	Frequency (n)	Prevalence (%)
Ethnicity		
Hispanic or Latino	35	5.2
Not Hispanic or Latino	609	90.6
Unknown/Not reported	28	4.2
Race		
American Indian /Alaskan Native	2	0.3
Asian	4	0.6
African	4	0.6
Caucasia/European	610	90.9
More than one race	26	3.9
Unknown /Not reported	26	3.9
Gender		
Male	35	5.2
Female	606	90.4
Non-binary	25	3.7
Not reported	6	0.9

Dysautonomia and Comorbid Conditions

The types of autonomic disorder and comorbid conditions can impact the diagnostic journey of the patient, as the symptom burden may differ, in some cases prompting patients and clinicians alike to more promptly pursue a diagnosis. Among the types of dysautonomia represented in our cohort, POTS was the most frequent (76.8%), followed by orthostatic hypotension, neurocardiogenic syncope, and inappropriate sinus tachycardia. In 7% of cases, a diagnosis was in progress, or the participant could not recall the specific type of dysautonomia. Immune-mediated autonomic dysfunction, either related to a rheumatological comorbidity (7.6%) or other autoimmune process (6.3%), was reported. Rarer forms of dysautonomia, such as pure autonomic failure, familial dysautonomia, autoimmune autonomic ganglionopathy, baroreflex failure, and multiple system atrophy, are also represented in this cohort (Table 3).

Dysautonomia is often accompanied by a myriad of symptoms, some of which result from comorbid conditions (Table 4). Among the comorbid conditions known to occur with dysautonomia, Ehlers-Danlos syndrome (EDS) was

Table 2. Types of Clinicians who Diagnosed Autonomic Dysfunction.

Diagnostic Clinician	Prevalence (%)
Cardiologist	53.0
Neurologist	26.5
Internal medicine clinician	6.1
Family medicine clinician	4.7
Other clinician	3.9
Pulmonologist	1.9
Geneticist	1.7
Rheumatologist	1.6
Gastroenterologist	0.6

Table 3. Types of Dysautonomia. Multiple Disorders/Conditions May Apply.

Autonomic disorder	Prevalence (%)
Postural orthostatic tachycardia syndrome	76.8
Orthostatic hypotension	18.2
Neurocardiogenic syncope	15.8
Inappropriate sinus tachycardia	13.1
I don't know /diagnosis in progress	8.0
Other dysautonomia	7.9
Secondary to rheumatological condition	7.6
Other immune-mediated dysautonomia	6.3
Pure autonomic failure	1.8
Familial dysautonomia	1.5
Autoimmune autonomic ganglionopathy	0.9
Baroreflex failure	0.9
Multiple system atrophy	0.1

Table 4. Comorbid Conditions.

Comorbid Conditions	Prevalence (%)
Ehlers-Danlos syndrome	42.9
Mast cell disorders	33.0
Vitamin E, B1, B3, B6, or B12 deficiency	29.6
Fibromyalgia	26.6
Myalgic encephalomyelitis/chronic fatigue syndrome	19.9
Other dysautonomia-related comorbid diseases	16.7
Hashimoto's thyroiditis	8.8
Sjögren's syndrome	7.7
Celiac disease	5.8
Diabetes	4.5
Chiari malformation	4.0
Systemic lupus erythematosus	2.1
Mitochondrial disease	1.8
Ulcerative colitis	1.3
Crohn's disease	1.2
Chronic inflammatory demyelinating polyradiculoneuropathy	1.2
Antiphospholipid syndrome	1.0
Delta storage pool deficiency	0.6
Charcot-Marie-Tooth disease	0.3
Sarcoidosis	0.1
Paraneoplastic syndrome	0.1
Parkinson's disease	0.0
Amyloidosis	0.0

the most common (42.9%), followed by mast cell disorders, deficiency of specific vitamins (ie, E, B1, B3, B6, or B12), fibromyalgia, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Several autoimmune conditions were reported, including Hashimoto's thyroiditis, Sjögren's syndrome, celiac disease, and systemic lupus erythematosus. Diabetes was reported at low frequency. 71.4% of EDS-affected participants also reported Chiari malformation. Other known conditions associated with autonomic dysfunction were reported with frequencies lower than 2.0%.

Discussion

The ANS plays a crucial role in the maintenance of homeostasis, regulating the internal organs and physiological functions, such as heart rate, blood pressure, respiration, sweating, pupillary dilation, digestion and sexual arousal.[4,34] Therefore, dysautonomia can impact any organ system in the body, causing significant morbidity. Several studies have reported protracted and tortuous diagnostic processes for dysautonomia patients[5,8,30]; this is in part due to the generalized presentation of autonomic symptoms, which overlap or mimic those associated with other conditions (e.g., headaches, pain, dizziness, constipation/diarrhea, and palpitations). However, if dysautonomia is suspected during a brief targeted examination, a subsequent comprehensive clinical assessment may be required.[8] Our study has shown that only approximately 10% of diagnoses are made by family medicine providers and internists combined, highlighting the need to expand the training of primary care providers to include the clinical presentation of autonomic dysfunction. Dysautonomia patients face multiple challenges pertaining to the diagnostic process: 1) their sometimes-generalized symptoms are often not promptly attributed to autonomic dysfunction and 2) access to a specialized testing center, often affiliated with larger academic medical institutions, is limited due to physical distance, cost of travel, wait time, or even unfamiliarity with the existence of these specialized centers.

Comorbid Conditions Can Impact the Diagnostic Journey of Dysautonomia Patients

Although POTS is the most common autonomic disorder in this cohort, this study differs from previously reported cross-sectional studies as it includes individuals affected by any form of autonomic dysfunction. We considered this broad inclusion approach because the morbidity associated with different types of autonomic disorders and their comorbidities can vary, with the more severe presentations likely prompting affected individuals to pursue a diagnosis more urgently. Additionally, people affected by orthostatic intolerance without tachycardia or with negative small nerve fiber biopsies may be more easily dismissed by some clinicians, despite enduring a heavy symptom burden. The inclusion of these individuals possibly explains our study's increased average time to diagnosis of 7.7 years compared to previous reports.

Immune-mediated forms of dysautonomia are also reported by nearly 14% of participants, albeit this is probably an underestimation, since specific autoantibodies are not systematically assayed.[35,36] Moreover, similarly to what was reported for POTS,[25] 27% of participants from our cohort report concomitant autoimmune and inflammatory conditions. The most common comorbid conditions are EDS, mast cell activation syndrome, fibromyalgia, and ME/CFS, which is consistent with the literature.[17,37,38] These

conditions can also be associated with a heavy symptom burden: patients affected by EDS, fibromyalgia, or ME/CFS live with chronic pain and fatigue, while mast cell disorders can cause allergic-like reactions which may result in anaphylaxis after exposure to a variety of triggers (eg, foods, fragrances, medication, or even stress).[17,39]

The co-occurrence of these conditions highlights the need for a collaborative approach among clinicians to support this patient population. Moreover, the recognition of the multiple known comorbid conditions may prompt clinicians to pursue an initial screening for autonomic dysfunction, thus facilitating the patient's diagnostic journey. Interestingly, cardiologists, not neurologists, diagnosed the autonomic disorder for more than half of the participants. This may reflect the heavy cardiopulmonary symptom burden of autonomic dysfunction, although patients also typically present with neurological symptoms such as dizziness, cognitive dysfunction (ie, brain fog), and headaches, which may not be immediately recognized by either the patient or the clinician. Additionally, cardiologists frequently evaluate patients for syncope, heart rhythm abnormalities, and palpitations, all of which could have etiologies other than autonomic dysfunction. Thus, cardiologists may encounter cases of cardiac dysautonomia during routine clinical evaluation. This may facilitate the diagnostic process of autonomic dysfunction, but it may preferentially accelerate diagnosis of autonomic disorders with a heavy cardiopulmonary burden than those without.

Psychological and Economic Impact of Dysautonomia

As with any chronic disease, a protracted time from symptom onset to diagnosis can have profound psychological and economic consequences for the patients and their families. Patients living with a chronic disease can experience heightened health anxiety related to their condition, which can negatively impact the social and health-related domains of quality of life. As a chronic disease that involves multiple organ systems, dysautonomia presents the unique challenge of orthostatic intolerance and/or syncope, which limits the ability to stand for prolonged periods of time, potentially impacting the ability to work and engage in social activities. Furthermore, the relationship between chronic disease, pain, and depression has been documented and should further be explored in this patient population.[40] People affected by multiple chronic diseases are more likely to experience severe pain, thus making them more likely to experience depression.[41] The burden of chronic disease also has important economic ramifications for the patients and their families. In 2016, chronic diseases had direct and indirect costs totaling over $3.7 trillion in the United States, an amount that has risen with increases in medical costs.[42] With respect to POTS, the most commonly studied autonomic disorder, the estimated economic costs associated with medical bills and lost employment exceed $10,000 for more than half of study participants.[14] Thus, a protracted time from symptom onset to diagnosis can have psychological and economic repercussions which can contribute to morbidity and aggravate dysautonomia symptoms.

Ongoing Efforts to Improve the Diagnostic Journey of Dysautonomia Patients

To reduce the burden of chronic diseases like dysautonomia, all efforts should be exhausted to reduce the delay in diagnosis to maximize treatment protocols and outcomes. This can include more comprehensive education and awareness of dysautonomia symptoms among healthcare providers to offer person-centered care. The rise in dysautonomia cases following the COVID-19 pandemic has in fact prompted dysautonomia non-profit organizations to raise funds and collaborate with established autonomic specialists to offer training programs for clinicians and patients and to improve awareness of dysautonomia and best practices for clinical management of this patient population.[43] The National Institutes of Health has released a Notice of Special Interest in August 2024 to stimulate research on POTS.[44] Furthermore, a delay in the diagnostic process may be reduced with greater access to basic screening tools to assess autonomic function outside of specialized testing centers. In general, a delay in accessing appropriate management strategies further compromises the individual's ability to function optimally and to access support services, compounding any underlying psychological challenge associated with morbidity and functional impairment.[45] In fact, autonomic disorders can often be clinically managed with disease-modifying therapies,[46] which may be more effective if initiated promptly. Thus, timely recognition and intervention of autonomic dysfunction has the potential to improve the patient's quality of life and prognosis and to reduce the economic impact of poorly managed chronic disease.

Limitations

As with any patient-reported outcome study, this study has some limitations. Although we asked participants to exclusively report formal diagnoses, participants may have incorrectly reported their conditions. To reduce ambiguity, we offered detailed lists of diagnoses and asked that participants only identify formal diagnoses made by their clinicians. Additionally, the diagnoses were made by different clinicians using potentially different criteria; thus, rarer forms of dysautonomia may be inconsistently diagnosed. Finally, social desirability bias can in principle always affect participant responses.[47]

Conclusion

The present study aims to characterize the diagnostic journey of dysautonomia patients using patient-reported data. Our study highlights the arduous journey of patients with an

autonomic disorder and the accompanying challenges of their diagnoses. The average time to diagnosis of 7.7 years (SD 10 years) in our cohort underscores the need for a better understanding of the clinical presentation of dysautonomia and comorbid conditions. The most frequently reported comorbid conditions are EDS, mast cell disorders, vitamin deficiency, fibromyalgia, and ME/CFS. While these conditions are known to affect this patient population, our study underscores the importance of evaluating patients affected by these conditions for dysautonomia to accelerate the diagnostic time. Finally, the present study provides insights to clinicians who are diagnosing and treating these patients, which could improve empathy. Future research is needed on best practices to help reduce time to diagnosis and better awareness by diagnosing clinicians. This includes the validation of survey instruments that can be employed by family medicine providers to rapidly assess dysautonomia-related symptoms, and those related to known comorbid conditions, such that referrals to cardiologists and neurologists can be made promptly.

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Author Contributions

John A. O'Dell, MSN, MBA: manuscript preparation, data analysis
Ash Walker, DHSc: study design, manuscript preparation
Andrew J. Latham, Ph.D.: study design, data analysis
Daniel J. Parisian, Ph.D.: data analysis, manuscript preparation
Lindsay E. Branch: data collection and analysis, manuscript preparation
Dreena D. Vanderburg: data collection and analysis, manuscript preparation
Ava A. Cox: data collection and analysis, manuscript preparation
Shelley Chavis: data analysis, manuscript preparation
Silvia E. Smith, Ph.D.: study design, data collection, data analysis, manuscript preparation.

Consent to participate

As this is a no greater than minimal risk study, Participants completed the informed consent process online with the option of contacting the Principal Investigator with any question. A copy of the signed Informed Consent Form was emailed to each Participant.

Consent for publication

Participants were informed in the Informed Consent Form that their deidentified responses would be used in publications. No identifying information is reported in this study.

Data availability

Deidentified data may be shared with the University of North Carolina at Pembroke IRB approval.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

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ORCID iD

Silvia E. Smith https://orcid.org/0009-0001-3981-4592

Supplemental Material

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