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Original Article

Dominant Transmission Observed in Adolescents and Families With Orthostatic Intolerance

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ABSTRACT

BACKGROUND: Orthostatic intolerance is typically thought to be sporadic and attributed to cerebral autonomic dysfunction. We sought to identify families with inherited autonomic dysfunction manifest as symptomatic orthostatic intolerance to characterize mode of inheritance and clinical features. **METHODS:** Sixteen families with two or more first- or second-degree relatives with autonomic dysfunction and orthostatic intolerance were enrolled. A clinical diagnosis of autonomic dysfunction defined by symptomatic orthostatic intolerance diagnosed by head-up tilt table testing was confirmed for each proband. Clinical features and evaluation were obtained from each proband using a standardized intake questionnaire, and family history information was obtained from probands and available relatives. **RESULTS:** Comprehensive pedigree analysis of 16 families (39 individuals with orthostatic intolerance and 40 individuals suspected of having orthostatic intolerance) demonstrated dominant transmission of autonomic dysfunction with incomplete penetrance. Affected individuals were predominantly female (71.8%, 28/39; F:M, 2.5:1). Male-to-male transmission, although less common, was observed and demonstrated to transmit through unaffected males with an affected parent. Similar to sporadic orthostatic intolerance, probands report a range of symptoms across multiple organ systems, with headaches and neuromuscular features being most common. **CONCLUSIONS:** Familial occurrence and vertical transmission of autonomic dysfunction in 16 families suggest a novel genetic syndrome with dominant transmission, incomplete penetrance, and skewing of the sex ratio. Elucidation of potential genetic contributions to orthostatic intolerance may inform therapeutic management and identification of individuals at risk. Adolescent evaluation should include identification and treatment of potential at-risk relatives.

Keywords: orthostatic intolerance, autonomic nervous system disease, primary dysautonomia, familial autonomic dysfunction, heredity, genetic, postural orthostatic tachycardia syndrome

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Conflicts of Interest: J.E.P. and J.R.L. are employees of the Department of Molecular and Human Genetics at Baylor College of Medicine; the Department has entered into a joint venture with the Baylor Genetics diagnostic laboratory. J.R.L. derives support through a professional services agreement with the Baylor Genetics. J.R.L. has stock ownership in 23andMe, is a paid consultant for Regeneron Pharmaceuticals, has stock options in Lasergen, Inc, and is a coinventor on multiple United States and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. M.T.N. is a consultant to Nonin Monitor (Minneapolis, MN). R.M., J.E.L., and I.J.B. have no interests to disclose.

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Introduction

Orthostatic intolerance typically presents as lightheadedness or dizziness in young adults and teenagers, but may also be manifest by symptoms of migraine, tachycardia, hypotension, fatigue, weakness, and nausea.[1,2] These symptoms have been attributed to the inability to maintain adequate venous return to the heart because of venous pooling, mostly in the lower body during upright position.[3] Orthostatic intolerance can result from autonomic nervous system dysfunction and is clinically characterized as neurally mediated (vasovagal) syncope, orthostatic hypotension, or postural orthostatic tachycardia syndrome (POTS).[1,4-7] Many individuals with orthostatic intolerance experience symptoms suggestive of multiorgan involvement, such as headaches, fatigue, lightheadedness, palpitations, joint pain, temperature intolerance, and nausea. This constellation of symptoms is consistent with a role for the autonomic nervous system throughout the body.[1,7] The head-up tilt table (HUTT) test, which enables measurements of blood pressure and heart rate during and after a change from supine to upright positioning, can be useful in both diagnosis of and distinction among different types of orthostatic intolerance.[5] The HUTT is also a useful tool for recapitulating the lightheadedness, fatigue, and nausea reported by many patients with orthostatic intolerance; significant hypotension, tachycardia, and syncope can be observed in severely affected individuals during testing. Somewhat paradoxically, patients can display a bradycardic response to HUTT, and cardiac asystole has been reported.[8-11]

Orthostatic intolerance is common, and estimates suggest that there are at least 500,000 individuals within the United States alone.[7] Although orthostatic intolerance can occur as an adverse medication effect or a manifestation of another disease, such as Parkinson disease or amyloidosis,[7] there are increasing reports of individuals with autonomic dysfunction for which there is no identifiable cause. Most patients represent isolated orthostatic intolerance cases and are thus thought to be sporadic, but there have been a few case reports for which multiple family members are affected,[12-14] with phenotypes ranging from orthostatic hypotension,[15,16] POTS together with functional gastrointestinal disease,[17] or vasovagal syncope.[18-23]

We describe 16 families for which at least two first- or second-degree relatives are affected with autonomic dysfunction defined by symptomatic orthostatic intolerance in the absence of any identifiable etiology or syndromic features. Clinical characteristics including detailed objective laboratory investigations and observed familial aggregation and segregation are described.

Patients and methods

Enrollment

Approximately 1000 sequential patients referred to the Dysautonomia Clinic at the University of Texas Health Science Center at Houston, McGovern Medical School between 2010 and 2015 were considered for inclusion in this study, which was approved by the institutional review boards for human research at the University of Texas Health Science Center and Baylor College of Medicine. During the time of the study, candidate index patients with a clinical diagnosis of autonomic nervous system dysfunction were chosen based on the presence of a positive family history and exclusion of a primary motor or sensory neuropathy, neurodegenerative disease, cerebral palsy, spinal trauma, autoimmune disease, mitochondrial disease, thyroid dysregulation, and diabetes mellitus. A total of 16 unrelated families were enrolled and available clinical information was collected for an additional 228 relatives. Each proband provided symptom and family history information and underwent a clinical evaluation, including objective laboratory investigations as described subsequently. Criteria for a clinical diagnosis of autonomic dysfunction were (1) evidence of orthostatic intolerance on HUTT evaluation performed and interpreted as previously described,[24] and (2) patient-reported symptoms of autonomic dysfunction. Patients with an abnormal HUTT evaluation but absence of symptoms during HUTT evaluation were excluded.

Genetic evaluation

Detailed three- or four-generation family histories were obtained by interview of the proband (or parent of proband if minor) and additional family members when available. Pedigrees were constructed using available information and used to assess potential inheritance patterns and penetrance of the autonomic dysfunction phenotype. For these analyses, probands and relatives meeting strict criteria for a clinical diagnosis of autonomic dysfunction (abnormal tilt table test and patient-reported symptoms of orthostatic intolerance in the absence of secondary causes) were classified and considered as affected (Figure, black symbols). Individuals with symptoms suggestive of autonomic dysfunction who had not undergone tilt table testing were also recorded (Figure, gray symbols).

Symptom assessment

For each proband, symptoms of autonomic dysfunction were assessed using a structured four-page symptom and history questionnaire organized by organ system (Supplemental Information). The questionnaire documented the presence and severity of 55 symptoms related to neurological, cardiologic, genitourinary, immunologic, gastrointestinal, musculoskeletal, and dermatologic systems. Severity of each symptom is rated by the patient on a scale of 0 to 4 with zero representing the absence of the symptom and “4” representing that the symptom occurs frequently and is severe. The questionnaire includes a detailed headache assessment that records duration and frequency of headaches, as well as severity assessed using the universal 10-point scale,[25,26] with a score of “0” indicating no pain and “10” indicating the most severe pain the patient has experienced. Genitourinary symptoms were not captured by the earliest version of the structured questionnaire and thus were not included in this study. For individuals less than 18 years of age, a parent or guardian completed the questionnaire (Supplemental Information). For relatives not locally available, telephone interviews were used to capture clinical features based on the components of the structured questionnaire.

Results

Demographics

A total of 16 index patients and their available relatives were enrolled in the study. Of these 16 families, 39 individuals had a clinical diagnosis of autonomic dysfunction based on the presence of symptoms of autonomic dysfunction and abnormal HUTT testing. Females were more frequently affected (71.8%, 28/39; F:M, 2.5:1). Forty additional individuals were suspected of having autonomic dysfunction based on reported symptoms but were unavailable for HUTT during the time frame of the study; this group was also predominantly female (70.0%, 28/40; F:M, 2.3:1). Ethnic or racial background was self-reported by each family and included mixed European Caucasian descent in 100% (16/16); one family additionally reported