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Autonomic Symptoms in Carriers of the m.3243A>G Mitochondrial DNA Mutation

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Abstract

Background: The m.3243A>G mutation can cause multisystem medical problems and can affect the autonomic nervous system.

Objective: To study the frequency and spectrum of autonomic symptoms associated with the m.3243A>G mitochondrial DNA point mutation.

Design, Setting, and Patients: We studied a cohort of 88 matrilineal relatives from 40 families, including 35 fully symptomatic patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS), 53 carrier relatives, and 16 controls using a questionnaire based on existing standard instruments for the evaluation of autonomic dysfunction. We compared the questionnaire with an expert evaluation. We compared data among the 3 groups using the Mantel-Haenszel χ^2 test to determine the statistical significance of differences between groups.

Results: Mutation carriers frequently had symptoms of autonomic dysfunction, specifically gastrointestinal and orthostatic intolerance.

Conclusions: Carriers of the m.3243A>G mutation have frequent autonomic symptoms. The m.3243A>G mutation should be considered as an etiological factor in patients with autonomic dysfunction and a medical or family history suggestive of mitochondrial disease. Because some autonomic symptoms are treatable, early detection and proactive management may mitigate the burden of morbidity.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a multisystem syndrome disease with progressive neurological decline that is punctuated

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by episodic neurological worsening.[1] The most common mutation underlying MELAS is the m.3243A>G mutation in the mitochondrial DNA.[2] Carriers of the m.3243A>G mutation without the strokelike episodes typical of MELAS can be asymptomatic or develop a broad range of signs and symptoms that can vary in severity and that are attributed to mitochondrial dysfunction.[3] The mutation may be more prevalent than previously thought, with a frequency reported to be as high as 236 cases per 100 000 individuals in an Australian population.[4] The mutation causes respiratory chain dysfunction and consequently impairs cellular energy metabolism. Neurons are extremely sensitive to cellular energy deficiency. As a result, both central and peripheral nervous systems are vulnerable in people harboring the m.3243A>G mutation. While central nervous system involvement is one of the hallmarks of MELAS, peripheral nervous system dysfunction can be subtle. We and others have previously reported clinical and subclinical evidence of peripheral neuropathy.[5,6] Our clinical experience suggests that autonomic nervous system dysfunction may be an important contributor to morbidity in MELAS.

We therefore hypothesized that m.3243A>G mutation carriers, both with and without the full MELAS syndrome, experience autonomic symptoms at a higher rate than the general population. Here, we describe the autonomic symptoms associated with the m.3243A>G mutation based on a cohort of 88 mutation carriers from 40 families using standardized questionnaires. This information will be useful to clinicians in diagnosing and managing patients with multisystem manifestations due to the m.3243A>G mutation.

METHODS

STUDY POPULATION

We evaluated a subset of consecutive m.3243A>G mutation carriers and their matrilineal relatives who are participating in an ongoing natural history study at Columbia University Medical Center, New York, New York. Participants are self-referred or physician-referred. Patrilineal or married-in relatives and friends were included as controls. Subjects (n=104) from 40 families were divided into 3 groups: m.3243A>G mutation carriers with lactic acidosis and with a history of strokelike episodes, focal seizures, or both were classified as fully symptomatic patients with MELAS (n=35); matrilineal carrier relatives without focal seizures or strokes were classified as carrier relatives (n=53); and patrilineal or married-in family members and friends were recruited as control subjects (n=16).

STUDY DESIGN

In a cross-sectional design, we coadministered an autonomic questionnaire adapted from the Autonomic Symptom Profile along with a comprehensive medical evaluation previously described.[7,8]

DETAILED DESCRIPTION OF STUDY PROCEDURES

The questionnaire consisted of 18 questions, each answered by yes or no. The questions targeted 14 symptoms in 7 domains of autonomic function (orthostatic, secretomotor, male sexual dysfunction, urinary, gastrointestinal, pupillomotor, and vasomotor), a detailed medication history, and a family history relevant to autonomic dysfunction. For the

orthostatic domain, in addition to inquiring about the presence of any orthostatic dizziness or lightheadedness, a positive response prompted additional, more specific questions to clarify the autonomic nature of these symptoms. This led to a more specific category of autonomic-type dizziness within the orthostatic domain. The questionnaire was administered by a single trained interviewer (K.E.). An expert in autonomic function who was blinded to group status (L.W.) interviewed a subset of patients and administered the same questionnaire, and we found excellent agreement between interviewers. Not all subjects answered all questions. The Table indicates the number of those who answered by question.

SETTING

All evaluations took place at the Columbia University Medical Center in New York.

DATA ANALYSIS

We compared data among the 3 groups using the Mantel-Haenszel χ^2 test to determine the statistical significance of differences between groups.[9] Comparisons between individual groups were performed using Bonferroni correction to adjust for multiple comparisons.

RESULTS

SUBJECTS

The 35 patients with MELAS had a mean age of 33 years (range, 11–61 years); 16 (46%) were men. The 53 carrier relatives had a mean age of 39 years (range, 8–69 years); 18 (34%) were men. The 16 control subjects had a mean age of 56 years (range, 23–73 years); 11 (69%) were men.

AUTONOMIC SYMPTOMS

Both patients with MELAS and carrier relatives commonly reported autonomic symptoms, and there was a statistically significant difference between the presence of any autonomic symptom in both groups and in control subjects ($P<.001$) (Table). Twenty-eight patients with MELAS (80%) and 33 carrier relatives (62%) reported 1 or more autonomic symptoms compared with 2 controls (12%). Nearly all autonomic symptoms were significantly more frequent in patients with MELAS than in controls, with the exception of dry eyes or mouth, a sensation of incomplete bladder emptying, and problems with male sexual performance. Carrier relatives reported significantly more gastrointestinal symptoms and problems with excessively cold or discolored hands and feet compared with controls (all $P<.05$).

Gastrointestinal symptoms were especially common in the MELAS and carrier groups. Twenty-three patients with MELAS (66%) and 20 carrier relatives (38%) reported 1 or more gastrointestinal symptoms compared with 0 controls. More than half of the patients with MELAS reported postprandial symptoms.

Orthostatic dizziness was reported by 15 patients with MELAS (43%) and more specific autonomic-type dizziness was reported by 10 patients with MELAS (29%), significantly more than carrier relatives and controls. Other orthostatic symptoms were reported by 9 of 31 patients with MELAS (29%) and 10 of 49 carrier relatives (20%) compared with 0

controls. This difference was statistically significant for the patients with MELAS compared with controls (P=.04).

Of the 28 patients with autonomic symptoms in the MELAS group, 8 (29%) were receiving medications that could interfere with autonomic function, compared with 10 of 33 (30%) in the carrier group and 2 of 2 (100%) in the control group. There was no significant difference between these groups (all P>.10). Of patients with autonomic symptoms, 5 (18%) in the MELAS group were receiving medications for diabetes mellitus, compared with 5 (15%) in the carrier group and 0 in the control group. Again, there was no significant difference between these groups (P>.99).

COMMENT

Autonomic symptoms have long been recognized as a feature of mitochondrial disorders such as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), Kearns-Sayre syndrome, and Leigh syndrome.[10] Symptoms presenting in infancy and severe enough to over-shadow myopathic abnormalities were found in 3 patients with mitochondrial encephalomyopathies.[11] In a series of 22 patients with a variety of mitochondrial diseases, only 4 patients reported autonomic symptoms, but 10 patients had autonomic dysfunction by laboratory investigation.[12] In a study of 33 patients harboring the m.3243A>G mutation, some measures of heart rate variability differed between patients and matched controls. Also, 4 of 7 patients who died during the 3-year study follow-up died suddenly and unexpectedly.[13] Similar differences in heart rate variability have been shown to be associated with an increased risk of cardiac mortality in patients following myocardial infarction.[14]

In addition to the increased risk that autonomic disturbances pose, their effect on quality of life may be substantial. In patients with paroxysmal atrial fibrillation, the secondary symptoms of dizziness, chest pain, and perspiration were predictive of low quality of life independent of the paroxysmal arrhythmia.[15] Patients with postural orthostatic tachycardia syndrome reported functioning comparable to that of patients with congestive heart failure or chronic obstructive pulmonary disease.[16]

To our knowledge, this series is the largest prospective, questionnaire-based study of autonomic dysfunction in a genetically homogeneous sample. We found that 80% of patients with MELAS and more than 60% of m.3243A>G carriers have 1 or more autonomic symptoms. Gastrointestinal symptoms were especially common in the MELAS group, occurring in 66% of these patients, and they occurred in almost 40% of mutation carriers. More than 40% of patients with MELAS reported orthostatic dizziness or lightheadedness. This pattern is consistent with our clinical experience in which these symptoms are both common and disabling. Nearly all symptoms questioned occurred significantly more frequently in the MELAS group compared with controls.

Our sample was limited to patients referred to our center and is not population based, so it may not be representative of the m.3243A>G population at large. In addition, our largely family-based control group is well matched for environmental and socioeconomic status but is poorly matched for age and sex. Because the incidence of autonomic symptoms increases

with advancing age, the older control group represents a potential confounder. However, the mismatch would result in an underestimate of the differences between patients and controls rather than false-positive conclusions.

Finally, the presence of diabetes mellitus and the use of concurrent medications with potential effects on the autonomic nervous system are potential confounders. However, we have taken a careful medication history and have established that both of the 2 control participants with autonomic dysfunction were receiving potentially causative medications compared with only approximately 30% in the carrier and MELAS groups. While there were more patients with diabetes mellitus in both the MELAS group and the carrier group, this difference did not reach statistical significance. This suggests that neither medication adverse effects nor diabetes mellitus alone can account for the relatively high prevalence of autonomic dysfunction symptoms.

In summary, our study suggests that autonomic symptoms are common among both patients with MELAS and m.3243A>G mutation carriers. Our data suggest that physicians might inquire about autonomic symptoms in patients with a medical or family history suggestive of mitochondrial disease because these symptoms affect quality of life, may be related to morbidity, and may respond to treatment. Further studies are needed to characterize the full extent of autonomic dysfunction in this population.

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REFERENCES

1. Ciafaloni E, Ricci E, Shanske S, et al. MELAS: clinical features, biochemistry, and molecular genetics. Ann Neurol. 1992;31(4):391–398. [PubMed: 1586140]
2. Goto Y, Nonaka I, Horai S. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature. 1990; 348(6302):651–653. [PubMed: 2102678]
3. Kaufmann P, Engelstad K, Wei Y, et al. Protean phenotypic features of the A3243G mitochondrial DNA mutation. Arch Neurol. 2009;66(1):85–91. [PubMed: 19139304]
4. Manwaring N, Jones MM, Wang JJ, et al. Population prevalence of the MELAS A3243G mutation. Mitochondrion. 2007;7(3):230–233. [PubMed: 17300999]
5. Kärppä M, Syrjälä P, Tolonen U, Majamaa K. Peripheral neuropathy in patients with the 3243A>G mutation in mitochondrial DNA. J Neurol. 2003;250(2):216–221. [PubMed: 12574954]
6. Kaufmann P, Pascual JM, Anziska Y, et al. Nerve conduction abnormalities in patients with MELAS and the A3243G mutation. Arch Neurol. 2006;63(5):746–748. [PubMed: 16682545]
7. Kaufmann P, Shungu DC, Sano MC, et al. Cerebral lactic acidosis correlates with neurological impairment in MELAS. Neurology. 2004;62(8):1297–1302. [PubMed: 15111665]
8. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. Neurology. 1999;52(3):523–528. [PubMed: 10025781]
9. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–748. [PubMed: 13655060]

10. Hirano M, Silvestri G, Blake DM, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): clinical, biochemical, and genetic features of an autosomal recessive mitochondrial disorder. Neurology. 1994;44(4):721–727. [PubMed: 8164833]
11. Zelnik N, Axelrod FB, Leshinsky E, Griebel ML, Kolodny EH. Mitochondrial encephalomyopathies presenting with features of autonomic and visceral dysfunction. Pediatr Neurol. 1996;14(3):251–254. [PubMed: 8736411]
12. Di Leo R, Musumeci O, de Gregorio C, et al. Evidence of cardiovascular autonomic impairment in mitochondrial disorders. J Neurol. 2007;254(11):1498–1503. [PubMed: 17987253]
13. Majamaa-Voltti KA, Winqvist S, Remes AM, et al. A 3-year clinical follow-up of adult patients with 3243A>G in mitochondrial DNA. Neurology. 2006;66(10):1470–1475. [PubMed: 16717204]
14. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation. 1992;85(1):164–171. [PubMed: 1728446]
15. van den Berg MP, Hassink RJ, Tuinenburg AE, et al. Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. Eur Heart J. 2001;22(3):247–253. [PubMed: 11161936]
16. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. Mayo Clin Proc. 2002;77(6):531–537. [PubMed: 12059122]

Table.

Subjects Who Responded Affirmatively to an Autonomic Symptom Questionnaire

Symptom[a]	Affirmative Responses/Total Responses, No. (%)		
	Patients With MELAS (n = 35)	Carrier Relatives (n = 53)	Controls (n = 16)
Dry eyes or mouth	7/35 (20)	14/53 (26)	2/16 (12)
Bouts of excessive saliva	8/35 (23)[b]	5/53 (9)	0/16 (0)
Any orthostatic dizziness	15/35 (43)[b,c]	9/52 (17)	0/16 (0)
Autonomic-pattern dizziness	10/35 (29)[b,c]	1/35 (3)	0/16 (0)
Standing-induced symptoms	9/31 (29)[b]	10/49 (20)	0/14 (0)
Excessively cold or discolored hands or feet; Raynaud phenomenon	15/34 (44)[b,d]	15/52 (29)	0/16 (0)
Intolerance of heat or cold	14/35 (40)[b]	12/53 (23)	1/16 (6)
Postprandial symptoms	17/33 (51)[b,c]	12/53 (23)	0/15 (0)
Unexplained abdominal pain and/or cramps	8/34 (23)[b]	9/53 (17)	0/16 (0)
Bouts of diarrhea	8/35 (23)[b]	4/53 (7)	0/16 (0)
Severe constipation	11/35 (31)[b]	9/53 (17)	0/16 (0)
Any gastrointestinal symptoms	23/35 (66)[b,d]	20/53 (38)	0/16 (0)
Bowel or bladder incontinence	10/34 (29)[b]	6/51 (12)	0/16 (0)
Sensation of incomplete bladder emptying	6/33 (18)	5/50 (10)	1/16 (6)
Problems with male sexual function	1/8 (12)	2/13 (15)	0/11 (0)
Pupillary dysfunction problems	14/35 (40)[b,c]	6/51 (12)	0/16 (0)
Any autonomic symptom	28/35 (80)[b,d]	33/53 (62)	2/16 (12)

Abbreviation: MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes.

[a] Symptoms listed are abbreviated from the complete questions posed to the subjects.

[b] Significant difference between patients and controls ($P < .05$).

[c] Significant difference between patients and carrier relatives ($P < .05$).

[d] Significant difference between carrier relatives and controls ($P < .05$).