Involvement of Cervical Muscle Lesions and Autonomic Nervous System in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

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Research article

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Abstract

Background: Patients with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) sometimes coincide with stiffness of cervical muscles. This study examined the effect of local modulation of the cervical muscles on ME/CFS and the underlying mechanism.

Methods: In total, 1,226 inpatients with ME/CFS who were resistant to outpatient care were enrolled in this study for 11 years. All patients underwent daily physical therapies to the cervical muscles during hospitalization. Self-rated records documenting the presence and absence of ME/CFS and the representative eight disorders that frequently accompany it at admission and discharge were compared. The pupil diameter was also measured to examine involvement of autonomic nervous system function.

Results: The recovery rate of ME/CFS after local therapy was 55.5%, and did not differ significantly by sex, age strata, and hospitalization period. The recovery rates of the eight disorders were variable (36.6–86.9%); however, those of ME/CFS in the disorder subpopulations were similar (52.3–55.8%). The recovery rates of all disorders showed strong associations with that of ME/CFS ($p<0.001$). The pupil diameter was decreased at discharge, and the change was significantly higher in the ME/CFS-recovered patients than ME/CFS-unrecovered patients in the total population and the subpopulations stratified by sex, age, and hospitalization period.

Conclusions: Local therapy to the cervical muscles led to recovery in more than half of patients with ME/CFS, at least partly through amelioration of the autonomic nervous system. There may be a causal relationship between recoveries of ME/CFS and these related whole-body disorders.

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Background

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a serious, chronic, and complex disease that occasionally affects the lives of patients due to debilitating fatigue [1–4]. It is accompanied by various symptoms throughout the body, such as headache, cervical stiffness, vertigo, cardiovascular and gastrointestinal disorders, fever of unknown etiology, and psychological disorders. The high prevalence and low employment rates of patients with ME/CFS impose an enormous burden on society. The Institute of Medicine of the National Academy of Sciences reported that ME/CFS affects up to an estimated 2.5 million people in the United States and generates direct and indirect expenses of approximately $17-$24 billion annually [5].

Since ME/CFS is a heterogeneous condition with a complex and multifactorial etiology, reaching a conclusive diagnosis using the current methods is difficult. Although several studies have suggested the involvement of abnormal widespread metabolites [6–8], infection and neurological disorders [9], calcium ion channels [10], or anaerobic thresholds [11, 12], the pathogenic mechanism of ME/CFS remains unclear. As such, patients are diagnosed through the exclusion of other conditions that could be responsible for the subjective symptoms with abnormalities across many domains [13. 14]. Thus, treatment remains symptom-based, multidimensional, and tailored to the needs of the individual patient [15, 16].

The symptoms of ME/CFS were recently reported to improve by the surgical treatment of cervical spine [17]. Patients diagnosed with ME/CFS occasionally have a history of trauma to the neck, such as whiplash-associated disorders (WAD) [18]. In our clinical experience, we have observed a potential trend of indefinite symptoms throughout the body including ME/CFS occasionally coinciding with stiffness or tenderness of the cervical muscles and proposed a new medical concept called “cervical neuro-muscular syndrome” [19]. For the treatment of the indefinite symptoms, we have tried local modulation of the cervical stiffness. Among physical therapies, low-frequency electrical stimulation [20, 21] and far-infrared irradiation [22] are reportedly effective at recovering muscle stiffness of the neck and shoulders. In fact, our previous study of patients with WAD showed that the combined application of these two physical therapies to the cervical muscles recovered not only local symptoms in the neck and shoulder, but also indefinite symptoms in the whole body [23]. Furthermore, our recent study of 1,863 patients with indefinite whole-body symptoms showed that therapies applied to the cervical muscles significantly improved signs and symptoms such as headache, cervical pain or stiffness, vertigo or dizziness, palpitation, dazzling, nausea or stomachache, fever of unknown etiology, and depression [24].

We propose autonomic nervous system involvement as the underlying mechanism. This system, which regulates the unconscious actions of the body via the sympathetic and parasympathetic nerves, reportedly plays a role in myalgic disorders such as fibromyalgia and low back pain [25, 26]. In contrast to the sympathetic nervous system’s excitatory role under a stressful situation, the parasympathetic nervous system oversees resting, recovery from stress, and maintenance of homeostasis. Several nuclei of the hypothalamus generate coordinated patterns of responses of the two systems to internal or social stressors [27]. To evaluate autonomic nervous system function, the pupil light reflex is known to be a representative indicator; the constrictor muscle of the pupil decreases its diameter under control of the ciliary ganglion, which is activated and innervated by a preganglionic autonomic nerve fiber [28–30]. In fact, the preliminary pupil light reflex test performed in a subpopulation of our recent study suggested possible autonomic nervous system dysfunction in the cervical muscles of patients with whole-body disorders [24].

The present study initially examined the effect of the two physical therapies to the cervical muscles in 1,226 patients with ME/CFS during hospitalization and examined the relationships between ME/CFS recovery and representative eight whole-body disorders that are frequently accompanied with ME/CFS. To learn the possible involvement of autonomic nervous system as an underlying mechanism, we further compared the changes of the pupil diameters during hospitalization between patients who did versus those without ME/CFS recovery.

Methods

Patients

Among patients who visited our institutions between May 2006 and May 2017 and were diagnosed with ME/CFS according to Fukuda's definition [13], we enrolled 1,363 patients who were resistant to outpatient care and required hospitalization. Outpatient care was variable and included pharmacological and behavioral strategies but did not include the application of physical therapies to the cervical muscles. In principle, hospitalization was decided by consent between patients and physicians independent of the severity of ME/CFS. The main reason for hospitalization was persistent symptoms that required more intensive treatments as well as detailed examinations of other organs. Discharge was also decided by consent between patients and physicians independent of the ME/CFS recovery by the definition above [13], mainly due to considerable improvement of symptoms of ME/CFS or related whole-body disorders. Patients who were hospitalized for 5-120 days were enrolled.

Intervention

All patients underwent low-frequency electrical stimulation and far-infrared irradiation applied to the cervical muscles for 15 minutes two or three times daily throughout the hospitalization period. No other treatments including medication, injection, external fixation, or cervical traction were performed. A combination of silver spike point (SSP; Nihon Medix, Chiba, Japan) and pain topra (LCF-30; Celcom, Inc., Fukuoka, Japan) was used for the low-frequency electrical stimulation, while a CERAPIA 3300 (Nihon Medix, Chiba, Japan) was used for the far-infrared ray irradiation.

For all participants, the self-rated records on the medical interview sheets documenting the presence or absence of the representative eight disorders that frequently accompany ME/CFS [1–4]; including headache, cervical pain or stiffness, vertigo or dizziness, palpitation, dazzling, nausea or stomachache, fever of unknown etiology, and depression, were collected at admission and discharge. Pupil diameter was also measured using a binocular infrared pupilometer (Iriscoder Dual C10641; Hamamatsu Photonics, Shizuoka, Japan) at admission and discharge, and each patient provided informed consent.

Statistical analysis

Statistical analyses were performed using SPSS 16.0J for Windows. *P* values less than 0.05 were considered statistically significant; all reported *p* values were two-sided. As the sample size (n = 1,226) was sufficient, the central limit theorem could be applied to confirm that the data were normally distributed and that violation of the normality assumption would not cause major problems [31]. Hence, the paired Student's t-test was used to examine the difference in the number of symptoms at admission versus discharge. The difference in the number of patients with each symptom between admission and discharge was evaluated using the chi-square test. The unpaired t-test was used to compare means between the recovered and unrecovered ME/CFS groups. In the univariate and multivariate logistic regression analyses, all variables were force entered into the multivariate model. Forward stepwise multivariate logistic regression analyses were also performed. The best model was selected based on likelihood ratio tests.

Results

Flow and backgrounds of participants

Figure 1 shows a flowchart of the patient enrollment process of the present study. A total of 1,363 patients who were diagnosed with ME/CFS according to the definition above [13] and hospitalized in our institutions were initially enrolled in this study. Of them, 137 were excluded after enrollment, including 42 who were discharged from the hospital after less than 5 days, 14 who were hospitalized for more than 120 days, 59 who were diagnosed with specific diseases in other organs after admission (one of whom died during hospitalization), seven who were transferred to other hospitals for treatment of specific diseases, five who refused to undergo pupil diameter measurement, and 10 who discharged themselves from the hospital based on their own judgement with unknown reasons. After the removal of these patients from the study population, 1,226 completed the study protocol. Among these patients, 680 (55.5%) were diagnosed as having recovered from ME/CFS according to the definition above [13] at discharge, while 546 (44.5%) remained unrecovered. The eight representative disorders accompanying ME/CFS and the pupil diameters were assessed and compared between the ME/CFS-recovered and -unrecovered groups.

Table 1 shows the baseline characteristics of the 1,226 participants (448 men, 778 women) with a mean age of 46.4 ± 16.3 years (mean ± standard deviation) and a mean hospitalization period of 62.5 ± 26.4 days. The recovery rate was not significantly altered by sex (men versus women), age strata (10–49 versus 50–89 years), or hospitalization period (5–60 versus 61–120 days) ($p > 0.05$).

Table 1
Baseline characteristics of study participants with versus without recovery

		Number (%)	Number (%)	Number (%)	
		Total	Recovered	Unrecovered	*P*-value
Variables		1,226 (100.0)	680 (55.5)	546 (45.5)	
Sex	Men	448 (36.5)	252 (56.3)	196 (43.7)	0.675
	Women	778 (63.4)	428 (55.0)	350 (45.0)	
Age strata (years old)	10–49	736 (60.0)	408 (55.3)	328 (44.7)	0.979
	50–89	490 (40.0)	272 (55.5)	218 (44.5)	
Hospitalization period (days)	5–60	518 (42.3)	276 (53.3)	242 (46.7)	0.188
	61–120	708 (57.7)	404 (57.1)	304 (42.9)	

Relationship between ME/CFS recovery and eight related disorders

Among the representative eight disorders accompanying ME/CFS [1–4], more than 70% of ME/CFS patients reported headache, cervical pain or stiffness, palpitation, dazzling, fever of unknown etiology, and depression; while 43.1% for vertigo or dizziness and 56.7% for nausea or stomachache (Table 2). The recovery rates of these disorders in the total population after physical therapies during hospitalization were variable: more than 70% in patients with vertigo or dizziness, nausea or stomachache, and depression; 50–70% in patients with cervical pain or stiffness, palpitation, dazzling, and fever of unknown etiology; and 36.6% in patients with headache. However, the recovery rates of ME/CFS among patients with the eight disorders were similar (52.3-55.8%) to that of the total population (55.5%). Furthermore, the chi-square test (Table 2) and logistic regression analyses (Table 3) between the recovery (versus non-recovery) of these disorders clearly showed a strong association with ME/CFS recovery in all disorders ($p < 0.001$). Among the disorders, the recovery from depression was most strongly associated with ME/CFS recovery (odds ratio, 13.70; Table 3).

Table 2
Number (percentage) of patients with versus without recovery according to the representative eight disorders accompanying ME/CFS

	Total (n = 1,226)	ME/CFS recovered	ME/CFS unrecovered	*P*-value
Headache	1,162 (94.8)	648 (55.8)	514 (44.2)	< 0.001
Recovered	425 (36.6)	314 (73.9)	111 (26.1)	
Unrecovered	737 (63.4)	334 (45.3)	403 (54.7)	
Cervical pain or stiffness	1,071 (87.4)	583 (54.4)	488 (45.6)	< 0.001
Recovered	606 (56.6)	414 (68.3)	192 (31.7)	
Unrecovered	465 (43.4)	169 (36.3)	296 (63.7)	
Vertigo or dizziness	528 (43.1)	285 (54.0)	243 (46.0)	< 0.001
Recovered	459 (86.9)	272 (59.3)	187 (40.7)	
Unrecovered	69 (13.1)	13 (18.8)	56 (81.2)	
Palpitation	960 (78.3)	502 (52.3)	458 (47.7)	< 0.001
Recovered	595 (62.0)	376 (63.2)	219 (36.8)	
Unrecovered	365 (38.0)	126 (34.5)	239 (65.5)	
Dazzling	979 (79.9)	536 (54.7)	443 (45.3)	< 0.001
Recovered	513 (52.4)	341 (66.5)	172 (33.5)	
Unrecovered	466 (47.6)	195 (41.8)	271 (58.2)	
Nausea or stomachache	695 (56.7)	378 (54.4)	317 (45.6)	< 0.001
Recovered	508 (73.1)	323 (63.6)	185 (36.4)	
Unrecovered	187(26.9)	55 (29.4)	132 (70.6)	
Fever of unknown etiology	1,045 (85.2)	554 (53.0)	491 (47.0)	< 0.001
Recovered	663 Z(63.4)	479 (72.2)	184 (27.8)	
Unrecovered	382 (36.6)	75 (19.6)	307 (80.4)	
Depression	894 (72.9)	470 (52.6)	424 (47.4)	< 0.001
Recovered	733 (82.0)	453 (61.8)	280 (38.2)	
Unrecovered	161 (18.0)	17 (10.6)	144 (89.4)	

Table 3
Odds ratio (95% CI) of the recovery (vs. non-recovery) of each disorder to that of ME/CFS by logistic regression analysis

	n	Odds ratio	95% CI	*P*-value
Headache	1,162	3.41	2.63-4.43	< 0.001
Cervical pain or stiffness	1,071	3.78	2.92-4.87	< 0.001
Vertigo or dizziness	528	6.27	3.33-11.78	< 0.001
Palpitation	960	3.26	2.48-4.28	< 0.001
Dazzling	979	2.76	2.13-3.57	< 0.001
Nausea or stomachache	695	4.19	2.92-6.02	< 0.001
Fever of unknown etiology	1,045	10.66	7.86-14.45	< 0.001
Depression	894	13.70	8.11-23.15	< 0.001
CI: confidence of interval				

Pupil diameter test

We further examined the possible involvement of autonomic nervous system function by comparing pupil diameters of admission and discharge (D-A) as well as the change ratio adjusted by the diameter at admission ([D−A]/A) (Table 4). In the total population, both change in pupil diameter (D−A=−0.046 ± 0.633 mm; mean ± standard deviation) and change ratio ([D−A]/A=−0.002 ± 0.123) decreased during hospitalization, suggesting improved autonomic nervous system function by the physical therapies. These decreases were strongly seen in ME/CFS recovered patients (D−A=−0.099 ± 0.700 mm, [D−A]/A= −0.011 ±

0.134); however, there were no decreases, but rather increases, in the unrecovered patients (D – A = 0.020 ± 0.532 mm, [D – A]/A = 0.009 ± 0.107). A statistical analysis of the total population revealed a significant difference in the change in pupil diameter between the recovered and unrecovered groups ($p = 0.001$ for D – A, and $p = 0.007$ for [D – A]/A), suggesting an association between autonomic nervous system function and ME/CFS recovery.

Table 4
Pupil Diameters (mm) at Admission and Discharge

		Total				ME/CFS recovered				ME/CFS unrecovered		
		Admission	Discharge	D-A	(D-A) / A	Admission	Discharge	D-A	(D-A) / A	Admission	Discharge	D
Variables		5.440 (1.034)	5.394 (1.050)	-0.046 (0.633)	-0.002 (0.123)	5.480 (1.063)	5.380 (1.076)	-0.099 (0.700)	-0.011 (0.134)	5.391 (0.997)	5.411 (1.017)	0 (
Sex	Men	5.621 (1.117)	5.541 (1.089)	-0.080 (0.621)	-0.008 (0.114)	5.672 (1.172)	5.520 (1.110)	-0.152 (0.666)	-0.019 (0.119)	5.555 (1.042)	5.567 (1.064)	0 (
	Women	5.336 (0.969)	5.310 (1.017)	-0.027 (0.640)	0.001 (0.129)	5.367 (0.977)	5.298 (1.047)	-0.068 (0.719)	-0.005 (0.142)	5.299 (0.960)	5.324 (0.980)	0 (
Age strata (years old)	10-49	5.807 (0.914)	5.772 (0.901)	-0.035 (0.637)	0.001 (0.118)	5.853 (0.949)	5.764 (0.930)	-0.089 (0.687)	-0.008 (0.126)	5.750 (0.866)	5.782 (0.865)	0 (
	50-89	4.889 (0.958)	4.827 (1.001)	-0.062 (0.629)	-0.006 (0.131)	4.920 (0.976)	4.806 (1.024)	-0.114 (0.721)	-0.015 (0.146)	4.850 (0.937)	4.853 (0.974)	0 (
Hospitalization period (days)	5-60	5.505 (1.044)	5.455 (1.042)	-0.050 (0.606)	-0.003 (0.112)	5.594 (1.085)	5.459 (1.076)	-0.135 (0.674)	-0.018 (0.117)	5.404 (0.988)	5.450 (1.005)	0 (
	61-120	5.393 (1.025)	5.349 (1.053)	-0.043 (0.653)	-0.001 (0.131)	5.401 (1.041)	5.326 (1.073)	-0.075 (0.717)	-0.005 (0.145)	5.381 (1.006)	5.380 (1.027)	-0 (

mean (standard deviation)

In subgroup analyses stratified by sex (men versus women), age strata (10-49 versus 50–89 years), and hospitalization period (5–60 versus 61–120 days), the decreases were reproducible in all subgroups except (D – A)/A of the women and young generation (10–49 years) groups. Just like the total population analysis, pupil diameter was significantly decreased in the recovered versus unrecovered patients independent of sex and age strata ($p < 0.05$), although the difference was not significant only in the longer hospitalization period (61–120 days) subgroup.

Discussion

This study is the first to show that the local therapies to the cervical muscles led to recovery in more than half of the patients with ME/CFS, suggesting that local modulation of the cervical muscles is a possible treatment for ME/CFS. Interestingly, however, among the representative eight disorders accompanying ME/CFS, the recovery rate of cervical pain or stiffness was lower (56.6%) than those of other systemic disorders such as vertigo or dizziness, nausea or stomachache, and depression (> 70%) (Table 2). This finding suggests that there might be other mechanisms independent of cervical muscle modulation. In fact, both electrical stimulation and far-infrared irradiation reportedly cause nerve regeneration and repair directly [32, 33]. Further studies using objective and quantitative measurements of muscle stiffness like the ultrasound elastography technique [34] may clarify the local therapy target.

As an underlying mechanism, we propose amelioration of the autonomic nervous system that passes through the cervical muscles by measuring pupil diameter. The canonical pathway that regulates the pupil diameter is such that the ganglion cell axons project to the Edinger-Westphal nucleus in the midbrain, where the preganglionic parasympathetic neuron fiber in oculomotor nerve which is activated and commands the constrictor muscle of the pupil [30]. Although the oculomotor nerve does not pass through the cervical muscles, another non-canonical pathway via the afferent parasympathetic neuron fiber in the vagus nerve, arising from the brainstem and extending through cervical muscles down to the thoracic and abdominal viscera [35], may be involved in the regulation of pupil diameter. Also, the sympathetic nerve reportedly enters the orbit via the divisions of the trigeminal nerve and a plexus of nerves surrounding the ophthalmic artery, a part of which commands the constrictor muscle of the pupil as a long ciliary nerve [36, 37]. In addition, here we measured pupil diameter without using a light stimulation as the indicator of autonomic nervous function. However, the pupil light reflex under light stimulation is known to be more sensitive [28, 29]. In fact, the pupil light reflex has been used to test patients with clinical signs of autonomic nerve dysfunction such as those with Parkinson's disease, Alzheimer's disease, and diabetes mellitus [38–40]. Although this study initially aimed to measure the pupil light reflex parameters under light stimulation, such as constriction rate and velocity, the institutional review board (IRB) did not allow us to deliver external stimulation that was not approved for the diagnosis or treatment of ME/CFS. In our recent study on patients with indefinite symptoms throughout the body, however, a subpopulation analysis of patients with dazzling exhibited a proportional improvement in the constriction rate and velocity with the pupil diameter without stimulation by local therapies [24]. Hence, we assume that pupil diameter measured without light stimulation could represent the pupil light reflex parameters with stimulation as an indicator of autonomic nervous system function.

The recovery (versus non-recovery) of all representative disorders accompanying ME/CFS showed a strong association with the recovery of ME/CFS ($p < 0.001$) (Table 3). Among them, the recovery from depression was most strongly associated with ME/CFS recovery (odds ratio, 13.70; Table 3). However, whether depression is causes or consequences of ME/CFS remains unclarified as previously reported [1, 4]. It is possible that local modulation of the cervical muscles by the physical therapy initially improves psychological disorders such as depression through the cerebral limbic system, which then leads to

recovery of the hypothalamus coordination of responses to sympathetic and parasympathetic nervous systems [27]. It is also noteworthy that the odds ratio of the recovery from dazzling, which is caused by the pupil light reflex dysfunction, to that from ME/CFS was the lowest (odds ratio, 2.755). Taken together, there may be a causal, although remains unclear, relationship between ME/CFS recovery and those of the related disorders through both autonomic nervous system dysfunction and other common pathologies.

Regarding the effect of the local therapies on ME/CFS, a limitation of this study is its lack of a control group of patients who did not undergo physical therapy to the cervical muscles. Although the participants did not receive any other interventions during the hospitalization, ME/CFS and the related disorders might possibly improve through resting alone. This project was initially planned as a prospective randomized controlled trial with two arms (with and without local therapy). However, neither the authorities of the Japanese Ministry of Health, Labour and Welfare nor the IRB granted permission to form a control group due to ethical problems, i.e. resting alone without interventions for hospitalized patients was not allowed. Notably, the patients enrolled in this study had already completed conventional outpatient care including resting at home for 12-91 days (mean, 49.3 days) before the hospitalization and were resistant to that care. Therefore, it seems improbable that more than half of the patients with ME/CFS would recover via resting alone, even during hospitalization.

Conclusions

Local therapy to the cervical muscles led to recovery in more than half of patients with ME/CFS, at least partly through amelioration of the autonomic nervous system. There may be a causal relationship between recoveries of ME/CFS and these related whole-body disorders. These findings suggest that the local modulation of cervical muscles may be a novel treatment for ME/CFS. However, the inpatient physical therapies performed in this study; two or three times daily for a mean of 62.5 days, is too costly for both health care providers and individuals. The development of more simple and feasible treatments is the next task. For the modulation of cervical muscles, we previously performed a prospective trial of the effects of an oral muscle-relaxant on ME/CFS. While the systemic modulation of muscle stiffness by the drug was somewhat effective at relieving local symptoms in the neck or shoulder, it had a minimal effect on whole-body disorders including ME/CFS (unpublished observation). Since we believe that local modulation of the cervical muscles independent of physical or medical intervention would effectively treat ME/CFS, we are now planning a clinical trial that will examine the effects of a topical muscle-relaxant poultice or ointment in patients with this disease.

Abbreviations

ME/CFS: myalgic encephalomyelitis / chronic fatigue syndrome; FIR: far-infrared irradiation; IRB: Institutional review board; SSP: silver spike point; whiplash-associated disorders; WAD: whiplash-associated disorders

Declarations

Ethics approval and consent to participate

The study was conducted with the approval of the institutional review board (IRB) of Tokyo Neurological Center and Matsui Hospital. All participants signed written consent to participate in the study. Written informed consent was obtained from a parent or guardian for participants under 16 years old. All rights of the patients were protected against any kind of disadvantage and individual matters.

Consent for publication

Not applicable. We are permitted to reproduce copyrighted materials.

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There was no funding associated with this study. The patients were hospitalized for intensive treatment and detailed examination, but not for this study. The cost of treatment was borne partly by the patients and partly by the Japanese national insurance.

Competing interests

The authors declare no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TM and KH conceived of the study idea. TM, KH, MI, YE, NS, and HK started the study. TM and HK obtained the ethical approval. TM, MI, YE, NS, SH, HF, MM, and HK acquired the data. TM, KH, and HK interpreted the data. TM and HK performed the statistical analysis. TM and HK wrote the initial manuscript. All authors revised the manuscript and approved the submitted version for publication.

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References

1. Komaroff AL. Advances in understanding the pathophysiology of chronic fatigue syndrome. JAMA. 2019 Jul 5. doi: 10.1001/jama.2019.8312. [Epub ahead of print]

2. Clark JE, Ng WF, Rushton S, Watson S, Newton JL. Network structure underpinning (dys)homeostasis in chronic fatigue syndrome; Preliminary findings. 2. PLoS One. 2019; 14: e0213724. doi: 10.1371/journal.pone.0213724. eCollection 2019.

3. Nacul L, de Barros B, Kingdon CC, Cli JM, Clark TG, Mudie K, Dockrell HM, Lacerda EM. Evidence of clinical pathology abnormalities in people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) from an analytic cross-sectional study. Diagnostics. 2019; 9: 41-56. doi:10.3390/diagnostics9020041

4. MorrisG, Maes M, Berk M, Puri BK. Myalgic encephalomyelitis or chronic fatigue syndrome: how could the illness develop? Metabolic Brain Disease. 2019; 34: 385–415. https://doi.org/10.1007/s11011-019-0388-6

5. Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Washington, DC: National Academies Press; 2015

6. Naviaux RK, Naviaux JC, Li K, Bright AT, Alaynick WA, Wang L, Baxter A, Nathan N, Anderson W, Gordon E. Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci USA. 2016; 113: E5472-E5480. doi:10.1073/pnas.1607571113

7. Nagy-Szakal D, Barupal DK, Lee B, Che X, Williams BL, Kahn EJR, Ukaigwe JE, Bateman L, Klimas NG, Komaroff AL, Levine S, Montoya JG, Peterson DL, Levin B, Hornig M, Fiehn O, Lipkin WI. Insights into myalgic encephalomyelitis/ chronic fatigue syndrome phenotypes through comprehensive metabolomics. Sci Rep. 2018; 8, 10056.

8. Mueller C, Lin JC, Sheriff S, Maudsley AA, Younger JW. Evidence of widespread metabolite abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav. 2020; 14: 562-572. doi:10.1007/s11682-018-0029-4.

9. Komaroff AL, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. 2011; 31: 325-337. doi:10.1055/s-0031-1287654

10. Cabanas H, Muraki K, Balinas C, Eaton-Fitch N, Staines D, Marshall-Gradisnik S. Validation of impaired transient receptor potential melastatin 3 ion channel activity in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients. Mol Med. 2019; doi: 10.1186/s10020-019-0083-4. [Epub ahead of print].

11. Stevens S, Snell C, Stevens J, Keller B, VanNess JM. Cardiopulmonary exercise test methodology for assessing exertion intolerance in myalgicencephalomyelitis/chronic fatigue syndrome. Front Pediatr. 2018; 6: 242. doi:10.3389/fped.2018.00242

12. Nelson MJ, Buckley JD, Thomson RL, Clark D, Kwiatek R, Davison K. Diagnostic sensitivity of 2-day cardiopulmonary exercise testing inmyalgic encephalomyelitis/chronic fatigue syndrome. J Transl Med. 2019; 17: 80. doi:10.1186/s12967-019-1836-0

13. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Int Med. 1994; 121: 953–959. doi:10.7326/0003-4819-121-12-199412150-00009

14. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute Of, Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an Illness. The National Academies Press. 2015. doi:10.17226/19012

15. Bested AC, Marshall LM. Review of myalgic encephalomyelitis/chronic fatigue syndrome: an evidence-based approach to diagnosis and management by clinicians. Rev Environ Health. 2015; 30: 223-249. doi: 10.1515/reveh-2015-0026

16. Rowe PC, Underhill RA, Friedman KJ, Gurwitt A, Medow MS, Schwartz MS, Speight N, Stewart JM, Vallings R, Rowe KS. Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: a primer. Front Pediatr. 2017. https://doi.org/10.3389/fped.2017.0012

17. Rowe PC, Marden CL, Heinlein S, Edwards CC 2nd. 17. Improvement of severe myalgic encephalomyelitis/chronic fatigue syndrome symptoms following surgical treatment of cervical spinal stenosis. J Transl Med. 2018; 16: 21. doi: 10.1186/s12967-018-1397-7

18. Tjell C, Iglebekk W, Borenstein P. Can a chronic BPPV with a history of trauma be the trigger of symptoms in vestibular migraine, myalgic encephalomyelitis/chronic fatigue yndrome (ME/CFS), and whiplash associated disorders (WAD)? A retrospective cohort study. Otol Neurotol. 2019; 40: 96-102.

19. Matsui T, Ii K, Hojo S, Sano K. Cervical neuro-muscular syndrome: discovery of a new disease group caused by abnormalities in the cervical muscles. Neurol Med Chir. 2012; 52: 75-80. https://doi:10.2176/nmc.52.75

20. Kang DH, Jeon JK, Lee JH. Effects of low-frequency electrical stimulation on cumulative fatigue and muscle tone of the erector spinae. J Phys Ther Sci. 2015; 27: 105-108.

21. Maneski LZ, Malešević NM, Savić AM, Keller T, Popović DB. Surface-distributed low-frequency asynchronous stimulation delays fatigue of stimulated muscles. Muscle Nerve. 2013; 48: 930-937.

22. Lai CH, Leung TK, Peng CW, Chang KH, Lai MJ, Lai WF, Chen SC. Effects of far-infrared irradiation on myofascial neck pain: a randomized, double-blind, placebo-controlled pilot study. J Altern Complement Med. 2014; 20: 123-129.

23. Matsui T, Iwata M, Endo Y, Shitara N, Hojo S, Fukuoka H, Hara K, Kawaguchi H (2019) Effect of intensive inpatient physical therapy on whole-body indefinite symptoms in patients with whiplash-associated disorders. BMC Musculoskelet Disord. 2019; 20: 251-258. https://doi: 10.1186/s12891-019-2621-1.

24. Matsui T, Hara K, Kayama T, Iwata M, Shitara N, Hojo S, Endo Y, Fukuoka H, Yoshimura N, Kawaguchi H. Cervical muscle diseases are associated with indefinite and various symptoms in the whole body. Eur Spine J. 2020 29: 1013-1021. doi: 10.1007/s00586-019-06233-5. Jan 14.

25. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther. 2007; 9: 216-223.

26. Gockel M, Lindholm H, Niemisto L, Hurri H. Perceived disability but not pain is connected with autonomic nervous system function among people with chronic low back pain. J Rehabil Med. 2008; 40: 355-358.

27. Benarroch EE. Physiology and pathophysiology of the autonomic nervous system. Continuum (Minneap Minn). 2020; 26: 12-24. doi: 10.1212/CON.0000000000000817.

28. Bremner F. 28. Pupil evaluation as a test for autonomic disorders. Clin Auton Res. 2009; 19: 88-101. doi: 10.1007/s10286-009-0515-2.

29. Wang Y, Zekveld AA, Naylor G, Ohlenforst B, Jansma EP, Lorens A, Lunner T, Kramer SE. Parasympathetic nervous system dysfunction, as identified by pupil light reflex, and its possible connection to hearing impairment. PLoS One. 2016; 11: e0153566.

30. Wilhelm H. Disorders of the pupil. Handb Clin Neurol. 2011; 102: 427-466.

31. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. Int J Endocrinol Metab. 2012; 10: 486-489. https://doi:10.5812/ijem.3505

32. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics. 2016; 13: 295-310. https://doi:10.1007/s13311-015-0415-1

33. Wang JL, Lin YC, Young TH, Chen MH. Far-infrared ray radiation promotes neurite outgrowth of neuron-like PC12 cells through AKT1 signaling. J Formos Med Assoc. 2019; 118: 600-610. https://doi:10.1016/j.jfma.2018.08.015

34. Illomei G. Muscle elastography in multiple sclerosis spasticity. Neurodegener Dis Manag. 2016; 6: 13-16. https://doi:10.2217/nmt-2016-0048

35. Bianca R, Komisaruk BR. Pupil dilatation in response to vagal afferent electrical stimulation is mediated by inhibition of parasympathetic outflow in the rat. Brain Res. 2007; 1177: 29-36.

36. Sinnreich Z, Nathan H. The ciliary ganglion in man (anatomical observations). Anat Anz. 1981; 150: 287-297.

37. Thakker MM, Huang J, Possin DE, Ahmadi AJ, Mudumbai R, Orcutt JC, Tarbet KJ, Sires BS. 37. Human orbital 37. sympathetic 37. nerve pathways. Ophthalmic Plast Reconstr Surg. 2008; 24: 360-366. doi: 10.1097/IOP.0b013e3181837a11.

38. Giza E, Fotiou D, Bostantjopoulou S, Katsarou Z, Karlovasitou A. Pupil light reflex in Parkinson's disease: Evaluation with pupillometry. Int J Neurosci. 2011; 121: 37–43. https://doi:10.3109/00207454.2010.526730

39. Fotiou DF, Stergiou V, Tsiptsios D, Lithari C, Nakou M, Karlovasitou A. Cholinergic deficiency in Alzheimer's and Parkinson's disease: Evaluation with pupillometry. Int J Psychophysiol. 2009; 73: 143-149. https://doi:10.1016/j.ijpsycho.2009.01.011

40. Lanting P, Heimans JJ, Reulen JP, Nauta J, van der Veen EA. Pupillary light reflex and quantitative sensory and motor neural function tests in diabetic patients. J Neurol. 1988; 235: 245–247.

Figures

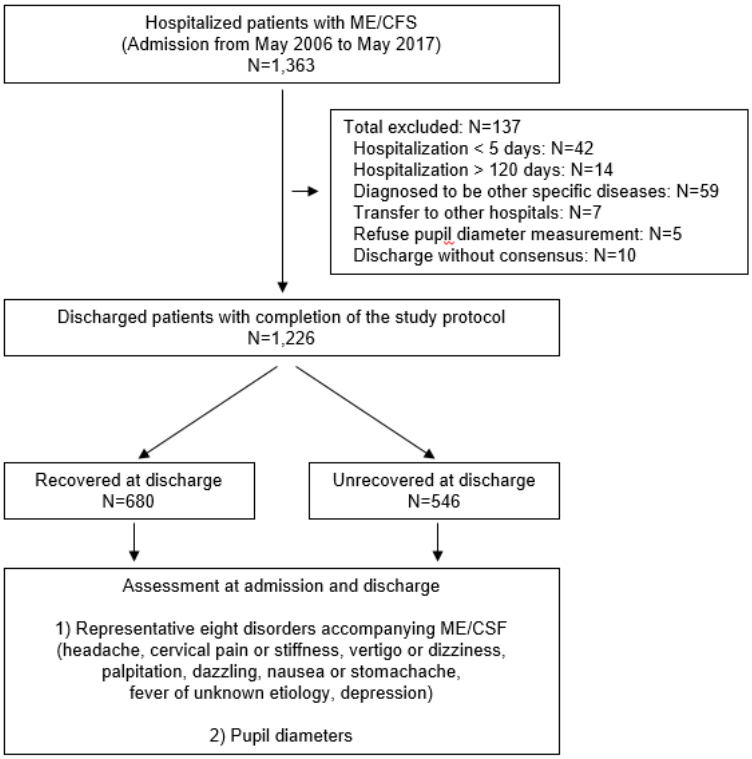

Figure 1

Flowchart of participant enrollment and study designs.