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THE CHRONIC FATIGUE SYNDROME AND HYPERVENTILATION

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Abstract—Chronic fatigue syndrome (CFS) is characterized by severe fatigue, lasting for at least 6 months, for which no somatic explanation can be found. Because hyperventilation can produce substantial fatigue, it seems worthwhile to investigate the relationship between it and CFS. It might be hypothesized that hyperventilation plays a causal or perpetuating role in CFS. CFS patients, non-CFS patients known to experience hyperventilation, and healthy controls were compared on complaints of fatigue and hyperventilation. CFS patients and non-CFS patients known to experience hyperventilation offered substantial complaints of fatigue and hyperventilation, both to a similar degree. Physiological evidence of hyperventilation was found significantly more often in CFS patients than in healthy controls. However, no significant differences between CFS patients with and CFS patients without hyperventilation were found on severity of fatigue, impairment, number of complaints, activity level, psychopathology, and depression. It is concluded that hyperventilation in CFS should probably be regarded as an epiphenomenon. © 1997 Elsevier Science Inc.

Keywords: Chronic fatigue syndrome; Fatigue; Hyperventilation.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as severe fatigue, lasting for at least 6 months, for which no somatic explanation can be offered. The pathogenesis of CFS is still unknown [1]. Because hyperventilation can produce substantial fatigue, and because fatigue is one of the main complaints in hyperventilation, it seems worthwhile to investigate their relationship. Grossman and de Swart [2] showed that 64% of the patients with hyperventilation syndrome complained of tiredness. In addition, the fatigue in hyperventilation [3] as well as in CFS [4–6] seems to be of a central type.

One might hypothesize that CFS is caused by hyperventilation. It is possible that stress causes hyperventilation, which in turn might lead to chronic fatigue. Another possibility is that hyperventilation plays a perpetuating role in CFS. Patients with

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CFS might develop hyperventilation due to their fatigue, and hyperventilation might in turn lead to an aggravation of fatigue.

Only a few studies have dealt with the relationship between CFS and hyperventilation. Rosen *et al.* [7] demonstrated hyperventilation in 38 of 40 patients suffering from CFS and claimed that hyperventilation plays an important role in the pathogenesis. Riley *et al.* [4], however, found no differences in the mean end-tidal P_{CO_2} both before and after exercise between 13 patients with CFS and 13 healthy controls. Saisch *et al.* [8] found evidence for hyperventilation in 9% of 31 CFS patients (29%). They did not find a relationship between the severity of hyperventilation and the degree of functional impairment, which was to be expected when hyperventilation would play a perpetuating role in CFS.

The first purpose of the present study is to determine whether there is any evidence for subjective complaints of hyperventilation in CFS, and whether there is evidence of fatigue in patients with hyperventilation. CFS patients and patients with known hyperventilation are compared to healthy controls to see whether these complaints are not only common but also specific for CFS and hyperventilation. The aim of the second part of the study is to determine whether there is any physiological evidence for hyperventilation in CFS and whether CFS patients show physiological evidence for hyperventilation more frequently than healthy controls. In the third part of the study, CFS patients with physiological evidence for hyperventilation (CFS HV) are compared to CFS patients without hyperventilation (CFS non-HV) on severity of fatigue, impairment, number of complaints, activity level, psychopathology, and depression, to determine the role of hyperventilation in CFS.

METHOD

Subjects

For the first part of this study, 39 patients with CFS and 32 healthy controls (all from a sample described elsewhere) [9], completed the questionnaires. The healthy controls were matched and recruited by a regional newspaper advertisement. Furthermore, 17 non-CFS patients with established hyperventilation (non-CFS HV) participated, all from the out-patient clinic of the Department of Pulmonology, Dekkerswald, University of Nijmegen. For the second and third parts of the study 27 CFS patients and the 32 healthy controls from the first part of the study participated. The experimental groups are not of an equal size because this study was linked to an already ongoing study.

All CFS patients were diagnosed at the General Internal Medicine out-patient clinic of the University Hospital, Nijmegen. CFS is defined as severe fatigue, lasting for at least 6 months, for which no somatic explanation can be offered. Patients were diagnosed with CFS if they fulfilled the Sharpe criteria [10]. According to these criteria, patients with a current diagnosis of major depression with melancholic or psychotic features, bipolar affective disorder, schizophrenia of any subtype, delusional disorders of any subtype, manic depressive illness, substance abuse, eating disorder, or proven organic brain disease (dementias of any subtype) were excluded.

Patients and healthy controls were diagnosed as having hyperventilation when they fulfilled three of the following criteria [11]:

- Low P_{aCO_2} in rest (<4.5 kPa).
- High breathing frequency, irregular breathing, or frequent sighing in rest.
- Decreasing P_{aCO_2} in control condition on a spirometer.
- Inverted ventilatory response to CO_2 .
- Adding CO_2 results in a regulation of breathing.
- One of the following criteria during or after the provocation test:
 - no step change in P_{etCO_2} when stopping voluntary hyperventilation;
 - no step change in respiratory frequency when stopping voluntary hyperventilation;
 - P_{aCO_2} 3 minutes after the end of the provocation $<90\%$ of the starting level.

Instruments

Subjective fatigue was measured with the subscale of subjective fatigue of the Checklist of Individual Strength (CIS) [12]. On this scale, the minimum score is 1 and the maximum score is 7.

Level of impairment was assessed with the Sickness Impact Profile (SIP) [13]. This questionnaire measures the influence of complaints in different areas of daily functioning. For this study, eight subscales were used (alertness behavior, sleep, homemaking, leisure activities, work, mobility, social interactions, ambulation).

Level of physical activity was assessed using an actometer. This apparatus is worn around the ankle for 2 weeks, recording the amount of movements every 5 minutes. This information is stored to an internal memory, and can be read by use of a personal computer [14].

Subjective complaints of hyperventilation were assessed by the Nijmegen Hyperventilation Questionnaire (NHQ) [15]. The cutoff score for hyperventilation is 23.

Psychopathology was measured with the Symptom Checklist (SCL-90R), an indicator of psychological disturbances, and the Beck Depression Inventory (BDI) [16, 17], a standardized self-report questionnaire for measuring depression.

Respiratory measurements were performed using a hyperventilation test in which the patient was connected to a closed spirometer circuit by a mouthpiece. A sampling capnograph measured P_{CO_2} in the respiratory air. Resting respiratory parameters were measured during 5 minutes: minute ventilation, P_{etCO_2} , breathing frequency, irregularity of breathing, and the time course of P_{etCO_2} during the first 5 minutes of the test. Next, some CO_2 was given in the inspiratory air, to raise P_{etCO_2} by 1.0 ± 0.2 kPa. The response of the ventilation to the increase in P_{etCO_2} was measured during another 5 minutes. Subsequently, the patient was disconnected from the spirometer, and only P_{etCO_2} was monitored during a 1-minute period of voluntary hyperventilation, and during the 3 minutes thereafter. The patients were asked whether they recognized their daily symptoms, during the hyperventilation. Finally, an arterialized capillary blood gas sample was taken to assess a possible metabolic acidosis, compensating for chronic hyperventilation.

Statistical analyses

The analysis of differences between groups on dichotomous variables was carried out with the chi-square test. Bonferroni correction was applied for the comparison of three experimental groups. Assuming a significance level of 0.05, a difference was considered significant if the $p < 0.017$. The analysis of differences between two groups on ratio variables was carried out with the *t*-test, with the significance level set at $p = 0.05$. The analysis of differences between more than two groups on ratio variables was performed by analysis of variance. Multiple comparisons were made by Duncan's multiple range tests, with $p < 0.05$.

RESULTS

First part

The mean age of the CFS patients was 36.5 (SD=8.8), of the non-CFS patients with known hyperventilation (non-CFS HV) 44.0 (SD=12.6), and of the healthy controls 37.0 (SD=12.8). Only the non-CFS HV patients differed significantly in age from the other two groups. There were no significant differences in gender: 80% of the CFS patients were female, as were 59% of the non-CFS HV patients and 84% of the healthy controls.

Data concerning subjective complaints of hyperventilation and subjective complaints of fatigue are presented in Table I. On the NHQ, 59% of the CFS patients scored above the cutoff score for hyperventilation. This is significantly different from healthy controls (3%), but not from non-CFS HV patients (65%). Non-CFS HV patients had a mean CIS score for subjective fatigue of 5.2. This is significantly different from healthy controls (2.0), but not from CFS patients (5.9).

Second part

The CFS patients and the healthy controls who underwent respiratory measurements did not differ significantly on age and gender. Mean age of the CFS patients

Table I.—Mean scores (SD) on subjective complaints of hyperventilation (NHQ), percent above the cutoff score for hyperventilation (NHQ > 23), and mean score (SD) of subjective fatigue (CIS) of 39 CFS patients compared to 17 non-CFS patients with known hyperventilation (non-CFS HV) and 32 healthy controls

	CFS	Non-CFS HV	Healthy
NHQ ^a	25.1	31.4 (11.6)	10.4 (6.3)
NHQ% > 23 ^b	59%	65%	3%
CIS subjective fatigue ^c	5.9 (1.1)	5.2 (2.2)	2.0 (1.1)

^a One-way ANOVA with Duncan multiple-range test ($p < 0.05$), CFS significantly different from non-CFS HV, and healthy controls, and non-CFS HV significantly different from healthy controls.

^b $p < 0.001$; CFS significantly different from healthy controls ($p < 0.001$), and non-CFS HV significantly different from healthy controls ($p < 0.001$); non-CFS HV is not significantly different from CFS.

^c One-way ANOVA, with Duncan multiple range test ($p < 0.05$), CFS significantly different from healthy controls, non-CFS HV significantly different from healthy controls; non-CFS HV is not significantly different from CFS.

was 36.6 (SD=8.0), and of the healthy controls 37.0 (SD=12.8). Seventy-eight percent of the CFS patients were female, compared to 85% of the healthy controls. Between CFS patients and healthy controls significant differences were found on fatigue, impairment, number of complaints, level of activity, subjective complaints of hyperventilation, and psychopathology, as expected [9] (Table II).

Table III shows the results of the respiratory measurements in CFS and healthy controls. Significantly more CFS patients showed hyperventilation (59%) than did healthy controls (22%). CFS patients differed from healthy controls on PetCO₂ and recognition of complaints, but not on the other respiratory parameters.

Third part

The 16 CFS patients with hyperventilation (CFS HV) and the 11 CFS patients without hyperventilation (CFS non-HV) were compared on subjective fatigue (CIS), impairment (SIP), number of complaints, activity level (actometer), subjective complaints specific for hyperventilation (NHQ score), psychopathology (SCL-90) and depression (BDI). No significant differences between groups were found

Table II.—Mean scores (SD) of 27 CFS patients and 32 healthy controls recruited for respiratory measurements, on subjective fatigue (CIS), impairment (SIP), number of complaints, activity level (actometer), subjective complaints of hyperventilation (NHQ), psychopathology (SCL-90), and depression (BDI)

	CFS	Healthy	<i>p</i> -value ^a
CIS subjective fatigue	5.9 (1.0)	2.0 (1.1)	< 0.001
SIP	17.1 (6.3)	1.2 (0.3)	< 0.001
Number of complaints	7.4 (3.7)	0 (0.0)	< 0.001
Actometer	25.1 (12.3)	36.4 (12.2)	< 0.001
NHQ	25.6 (11.3)	10.4 (25.6)	< 0.001
SCL-90	155.4 (27.2)	106.9 (22.0)	< 0.001
BDI	10.6 (5.3)	2.7 (4.0)	< 0.001

^a Using the *t*-test.

Table III.—Mean scores (SD) or percentage on respiratory measurements in 27 CFS patients and 32 healthy controls

	CFS	Healthy	<i>p</i> -Value
Petco ₂ (kPa) ^a	4.5 (0.66)	4.9 (0.40)	< 0.005
Petco ₂ < 4.5 ^b	52%	22%	< 0.05
Paco ₂ ^a	4.75 (0.69)	4.83 (0.57)	NS
Breathing frequency ^a	13.1 (3.7)	15.1 (3.7)	NS
Tidal volume	0.604 (0.20)	0.560 (0.18)	NS
Decreasing Petco ₂	36%	22%	NS
Irregular breathing ^b	30%	16%	NS
Delayed recovery after Provocation ^b	56%	38%	NS
Recognition ^b			
None	41%	81%	< 0.01
Partly	37%	13%	< 0.01
Completely	22%	6%	< 0.01
Hyperventilation, according to physiological criteria ^b	59%	22%	< 0.005

^a Using the *t*-test.^b Using the chi-square test.

(Table IV). CFS HV patients as well as CFS non-HV patients were both extremely fatigued and impaired. There was neither a significant difference in the number of complaints, nor the level of activity or subjective complaints of hyperventilation. Finally, CFS-HV patients and CFS non-HV patients did not differ on psychopathology and depression.

DISCUSSION

Patients with CFS endorsed subjective complaints of hyperventilation, similar to non-CFS patients with known hyperventilation. The latter showed substantial fatigue, of similar severity as CFS patients. Physiological evidence for hyperventilation was found significantly more often in CFS patients (59%) than in healthy controls (22%), with a significant difference in the mean resting Petco₂. Rosen et al. [7] found hyperventilation in 93% of the CFS patients and 55% of the healthy controls,

Table IV.—Mean scores (SD) of 16 CFS patients with hyperventilation (CFS HV) and 11 CFS patients without hyperventilation (CFS non-HV) on subjective fatigue (CIS), impairment (SIP), number of complaints, activity level (actometer), subjective complaints of hyperventilation (NHQ), psychopathology (SCL-90), and depression (BDI)

	CFS HV	CFS non-HV	<i>p</i> -Value ^a
CIS subjective fatigue	5.8 (1.0)	6.0 (0.9)	NS
SIP score	18.2 (6.1)	16.4 (6.5)	NS
Number of complaints	8.1 (3.6)	6.5 (3.7)	NS
Actometer	24.1 (10.2)	26.6 (15.2)	NS
NHQ	25.6 (8.2)	25.5 (15.4)	NS
SCL-90	153.9 (28.1)	157.9 (27.1)	NS
BDI	10.1 (4.0)	11.4 (6.9)	NS

^a Using the *t*-test.

whereas Saisch *et al.* [8] found evidence for hyperventilation in 29% of the CFS patients, and Riley *et al.* [4] found no differences in the mean P_{etCO_2} between CFS patients and healthy controls. These conflicting findings can be explained by the differences in the criteria used in diagnosing hyperventilation. In the study by Rosen *et al.* [7], less stringent criteria were used. Patients were also diagnosed with hyperventilation if they had a positive "think test": 3 minutes after the hyperventilation provocation test, patients were requested to close their eyes and think about the circumstances of an attack and the feelings and sensations experienced. A fall of end-tidal P_{aCO_2} of 1.3 kPa or more was taken as a positive response [18]. However, the resting P_{etCO_2} in that study did not differ between CFS patients and healthy controls, as in the study of Riley *et al.* [4]. In the study by Saisch *et al.* [8], the criteria were more strict than in our study. Patients were diagnosed with hyperventilation only if the P_{etCO_2} was less than 4.0 kPa at rest, during or after exercise, or at 5 minutes after the end of voluntary overbreathing. Using the criterion of a P_{etCO_2} of less than 4.0 kPa, in our study, 19% of the CFS patients and none of the healthy controls were diagnosed with hyperventilation. This is closer to the finding of 29% hyperventilating CFS patients found in the study by Saisch *et al.* [8].

If hyperventilation plays an important role in the pathogenesis or perpetuation of CFS, one would assume that hyperventilation is common in CFS, and one would expect higher scores of fatigue and impairment in the CFS patients with hyperventilation, compared to the CFS patients without hyperventilation. Like Saisch *et al.* [8], we found physiological evidence for hyperventilation in some of the CFS patients, the exact percentage depending on the criteria used. In addition, we could show that the high percentage of 93% found in the study by Rosen *et al.* [7] could be explained by the less strict criteria used: hyperventilation in CFS is not as common as they suggest. Comparing CFS patients with hyperventilation to CFS patients without hyperventilation, no differences on fatigue and impairment were found, as in the study by Saisch *et al.* [8]. There were also no differences found on variables such as the number of complaints, level of activity, psychopathology, and depression. If hyperventilation plays a role in CFS, one would at least expect some differences. Using the strict criteria of a 4.0 kPa P_{aCO_2} at rest, five of our CFS patients showed hyperventilation. However, even then, no differences are found between CFS patients with and CFS patients without hyperventilation. Therefore, it is unlikely that hyperventilation plays a role in the pathogenesis or perpetuation of CFS.

Depending on the criteria one uses, it can be said that signs of hyperventilation were found in a substantial number of the CFS patients. Furthermore, non-CFS HV patients had significantly more complaints of fatigue than healthy controls. However, we did not find more complaints of fatigue in hyperventilating CFS patients than in non-hyperventilating CFS patients. Therefore, hyperventilation is probably an epiphenomenon in CFS, and does not play a substantial causal or perpetuating role.

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