Association Between Oxidative Damage Markers and Self-Reported Temporomandibular Dysfunction Symptoms in Patients with Chronic Fatigue Syndrome

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ABSTRACT. Full blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haematinics and markers for oxidative stress were measured on thirty-three patients diagnosed with chronic fatigue

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The authors are grateful to the staff of the Hunter Area Pathology Service for the estimation of full blood count and serum vitamin B_{12}, ferritin and iron and the University of Newcastle, including Dr. R. H. Dunstan, for their constructive comments. They also thank the Gideon Lang Foundation, the Judith Mason CFS Research Grant and the Lower Hunter CFS/ME Fundraising Association for their financial support and members of the Hunter Valley branches of the ME/CFS society of NSW for their support and encouragement.

Journal of Chronic Fatigue Syndrome, Vol. 12(3) 2004
Available online at http://www.haworthpress.com/web/JCFS

doi:10.1300/J092v12n03_04

syndrome (CFS) and twenty-seven age and sex matched controls. The CFS patients had increased prevalence of symptoms of temporomandibular dysfunction (TMD). Jaw muscle pain was associated with increases in methaemoglobin ($P < .002$), ferritin ($P < .02$) and malondialdehyde ($P < .007$) whilst temporomandibular joint (TMJ) clicking and/or locking was associated with increases in methaemoglobin ($P < .001$), malondialdehyde ($P < .05$) and vitamin B_{12} ($P < .02$) levels. Multiple regression analysis found methaemoglobin to be the principle component associated with TMD symptoms in the CFS patients. Increases in scalar severity responses to jaw muscle pain and TMJ clicking and/or locking were positively correlated with methaemoglobin by multiple regression. These data indicate that oxidative stress due to excess free radical formation was associated with jaw muscle pain in CFS patients and suggest that these symptoms were likely to be associated with a pathogen-associated aetiology.

KEYWORDS. Oxidative damage, methemoglobin, malondialdehyde, vitamin B_{12}, TMD syndrome, chronic fatigue syndrome, pain aetiology, TMD aetiology

INTRODUCTION

Temporomandibular dysfunction (TMD) is a common disorder in the community with up to 48% of the population having palpable muscle pain, 20% reporting pain to be continually present, and 4-5% seeking treatment (1). Treatment seeking is associated with increased pain severity and distribution and is more common for female patients (2). Chronic TMD pain occurs in increased prevalence in Chronic Fatigue Syndrome (CFS) and Fibromyalgia Syndrome patients but appears to represent a distinct clinical set of entities (3). The majority of TMD pain patients report a gradual onset (4,5) and they have an increased prevalence of infectious events at onset (4). No laboratory test has been developed to assist in the diagnosis for these conditions. Richards et al.

reported alterations in erythrocyte morphology and markers of oxidative stress to be associated with symptom presentation in CFS patients (6, 7). Importantly the level of methaemoglobin was associated with jaw muscle pain in CFS patients (8). Aghabeigi et al. (9) reported altered lipid and aspirin metabolism in chronic TMD pain patients suggestive of increased free radical production, however the measures used in that study were not related to joint pain. This study investigates whether TMD symptoms in CFS patients are associated with alterations in blood cell and oxidative parameters.

METHODS

Participants

Thirty-three patients with CFS and twenty-seven control subjects were recruited over a 30-month period from June 1995 to December 1997, as previously reported (8). The CFS group comprised patients who had been previously diagnosed by medical practitioners as having CFS according to standard criteria (1,2), and formed part of a larger study on chronic fatigue syndrome and rheumatoid arthritis (6,7). Recruitment was facilitated by the Lower Hunter ME/CFS Support Group and the subject samples were blinded for analysis. Controls were age and gender matched persons not from the patient's immediate family and did not suffer from any of the defined CFS symptoms. The protocols for this project were approved by the University of Newcastle Human Research Ethics Committee.

Questionnaire

All subjects were provided with a questionnaire addressing onset events, symptom incidence, pain distribution, medical history and duration and severity of symptoms. Symptom indices were established as described previously (4) to assess the association of patient symptom expression and the morphological parameters measured. The question-

naire symptoms represent the self-reporting of the symptoms within the previous 7-days.

Blood Sampling

Samples were taken from an antecubital vein by an experienced phlebotomist without trauma using a plastic 20 mL syringe and 21 g needle. Specimens were placed in appropriate anticoagulant immediately upon withdrawal of the needle. Ten millilitres of blood were anticoagulated with EDTA for assessment of whole blood viscosity (WBV), erythrocyte folate (folate) and methaemoglobin (MetHb). Ten millilitres were anticoagulated with heparin for assessment of erythrocyte malondialdehyde (MDA), erythrocyte reduced glutathione (GSH) and erythrocyte 2, 3-diphosphoglycerate (DPG). Five millilitres of blood were allowed to clot in a plain tube for assessment of C-reactive protein (CRP), serum ferritin, serum iron, total iron binding capacity, and serum vitamin B_{12} estimation. A further 5 mL of blood was anticoagulated with EDTA for full blood count (FBC) and erythrocyte sedimentation rate (ESR).

Blood Cell and Oxidative Markers

MDA, GSH, DPG, MetHb, FBC, ESR, CRP and WBV at 0.1 sec^{-1} [WBV low shear rate (LSR)] and 100 sec^{-1} [WBV high shear rate (HSR)] were measured as previously described (7). The FBC consisted of the following tests: Total leucocyte count (WCC), total erythrocyte count (RBC), haemoglobin concentration (Hb), haematocrit (Hct), Mean erythrocyte volume (MCV), mean erythrocyte haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and erythrocyte distribution width (RDW).

Serum iron (S.Fe) and total iron binding capacity (TIBC) were performed on a Hitachi 747 ™ blood chemistry analyser. Saturation of iron binding proteins (% Saturation) was calculated from these parameters. Serum ferritin (ferritin), serum vitamin B_{12} (S.B12) and erythrocyte folate (folate) were assayed using the Sanofi Access™ chemiluminescence analyser.

Statistical Analysis

The blood parameters (log or arcsine transformed) and the clinical data were analysed using Student's *t*-test, Mann-Whitney U, Spearman rank and Pearson product-moment correlations, standard and forward stepwise discriminant function or multiple regression analysis and odd ratios. The data were processed using Microsoft ® Excel 97 (Microsoft Corporation) and Statistica v5.1 (Statsoft, Tulsa).

RESULTS

Patient Characteristics and TMD Symptoms

Patient demographic information is summarised in Table 1. All study subjects were of Caucasian Western European ethnic origin. Table 1 also shows the prevalence facial muscle pain and temporomandibular joint (TMJ) symptoms as individual and combined measures in the CFS and control groups. In addition, the prevalence of scalar response scores for these TMD symptoms are provided for both groups in this table. The CFS patients had an increased prevalence and severity of individual and combined TMD symptoms compared with the control group. Only 21% of the CFS patients reported both facial and TMJ pain whilst none of the control subjects reported face pain. Thus, the CFS patients had an increased prevalence and severity of 7-day self-reported TMD symptoms compared with the control subjects.

TMD Symptoms, Blood Cell and Biochemical Parameters

Facial Pain

The CFS patients were divided into two subsets with (FP-CFS) or without facial pain (CFS) and these two subsets were compared with

TABLE 1. Patient Demographics and TMD Symptom Distribution Data.

Characteristic	**CFS**	**Control**	***P***
Age in years (range)	40.8 (12-74)	36.1 (15-60)	NS
Number of subjects	33	27	
Percentage female	20 (60.6%)	14 (51.9%)	NS
Duration in months (range)	114.5 (12-360)	N/A	–
TMD Symptoms			
Prevalence	N(%)	N(%)	
Face pain	17(51.5)	0	<.001
TMJ click/lock	12(36.4)	1(3.8)	<.003
Combined Prevalence			
Nil	11(33.3)	26(96.3)	<.001
TMJ click/lock	10(30.3)	1(3.8)	<.009
Face pain	5(15.2)	0	<.04
Face pain & TMJ click/lock	7(21.2)	0	<.01
Scalar Score (0-4)	**MEAN (SD)**	**MEAN (SD)**	
Face pain	.97(1.2)	0	<.001
TMJ clicking/locking	.79(1.2)	0.12(0.59)	<.004

Prevalence (%) of Scalar Responses (range 0-4)	**FP**	**TMJ**	**FP**	**TMJ**	**FP** *P*	**TMJ** *P*
0	48.5	63.6	100	96.2	<.001	<.003
1	27.3	12.1	0	0	<.02	NS
2	6.1	12.1	0	0	NS	NS
3	15.2	6.1	0	3.8	<.04	NS
4	3.0	6.1	0	0	NS	NS

Statistical methods: t-test and χ^2 test; FP = face pain; TMJ = TMJ clicking and or locking; N/A = not applicable; SD = standard deviation.

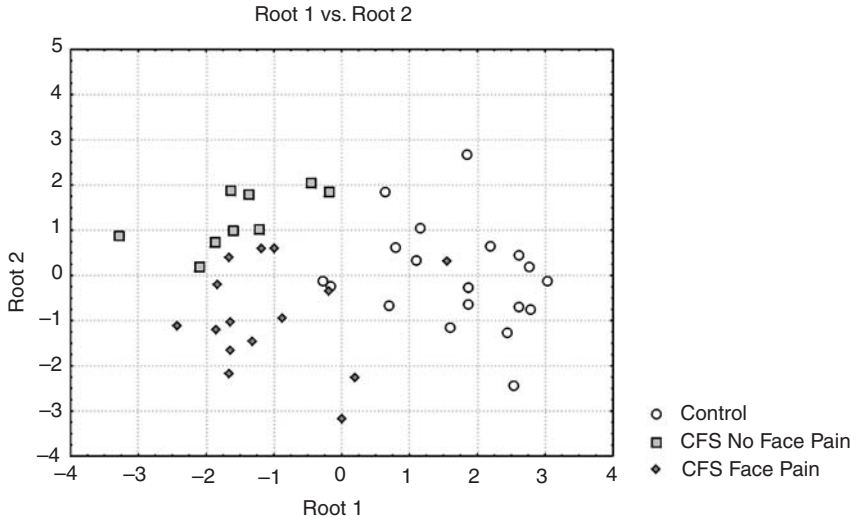
the control subjects. Three biochemical parameters, methaemoglobin, ferritin and malondialdehyde were elevated in the FP-CFS patients compared with the controls and CFS patients, as shown in Table 2. The discriminant function analysis comparing the blood biochemistry profiles between the controls, CFS and FP-CFS groups indicated that these three groups had different biochemistry profiles ($P < .002$), where methemoglobin was the primary discriminant variable. Figure 1 shows the good separation of control, CFS and FP-CFS subjects in the canonical scatter plot generated by the discriminant function analysis.

TABLE 2. Summary of the uni- and multi-variate analyses of the differences in the blood cell parameters and the oxidation measures between the CFS patients with TMD symptoms, the remaining CFS patients and control subjects.

Face pain					
Parameter	**Control (C)**	**CFS**	**FP-CFS**	**ANOVA**	**FP-CFS vs. C**
Number (n =)	*27*	*16*	*17*	NS	NS
Age (± SD)				< .05	< .04
% female	51.9	75.0	47.1		
	(± SD)	(± SD)	(± SD)		
MetHb	.62(.74)	.77(.72)	1.86(1.71)	< .002	< .002
Ferritin	86.3(84.4)	86.0(94.4)	143.8(192.2)	< .02	NS
MDA	31.3(15.1)	43.0(23.8)	50.4(24.2)	NS	< .007
Forward Stepwise Discriminant Function Analysis					
Model: Wilks' λ = 0.287, F(20,62) = 2.682, P < 0.002					
Variables: (1) Methaemoglobin, (2) WBV(HSR), (3) Malondialdehyde					
TMJ Clicking/Locking					
	Control (C)	**CFS**	**TMJ-CFS**	**ANOVA**	**TMJ-CFS vs. C**
Number	*27*	*20*	*12*		
Age (± SD)		45.2	36.6	< .03	NS
% female	51.9	52.6	75.0	NS	NS
	(± SD)	(± SD)	(± SD)		
MetHb	.62(.74)	.77(.72)	1.86(1.71)	< .001	< .001
MDA	31.3(15.1)	43.0(23.8)	50.4(24.2)	< .05	< .03
S.B12	283(120)	340(194)	335(127)	NS	< .05
Forward Stepwise Discriminant Function Analysis					
Model: Wilks' λ = 0.324, F(12,30) = 5.226, P < 0.0001					
Variables: (1) Methaemoglobin, (2) Ferritin, (3) Glutathione					

Univariate analysis: ANOVA and Tukey HSD test: NS = Not statistically significant.
Abbreviations: MetHb = methaemoglobin, MDA = malondialdehyde, S.B12 = serum vitamin B_{12}, WBV(HSR) = whole blood viscosity (high shear rate).

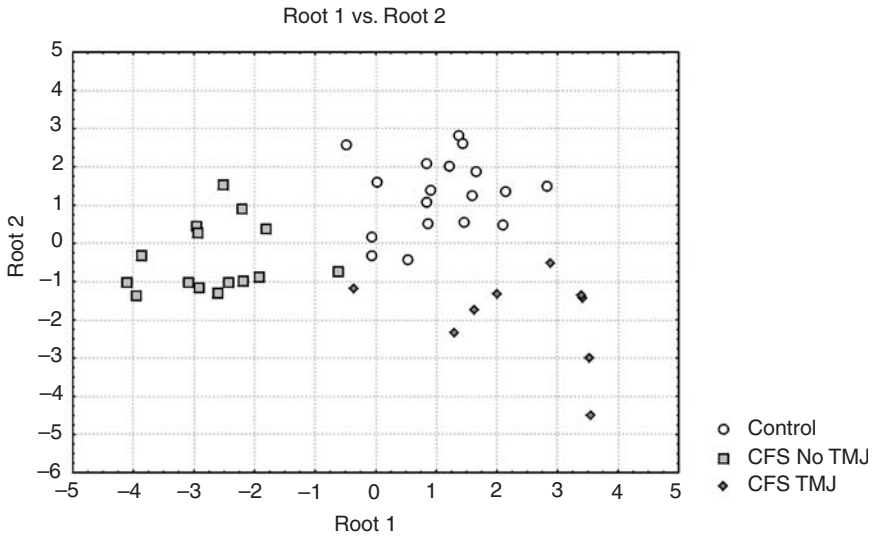
FIGURE 1. Canonical scatter plot of the variation in the measured red blood cell and oxidative markers in the control subjects and the CFS patients with and without face pain.



TMJ Pain

The chronic fatigue syndrome patients were then divided into two subsets with (TMJ-CFS) or without TMJ clicking/locking (CFS). Two biochemical parameters, methaemoglobin and malondialdehyde, were elevated in the TMJ-CFS patients compared with the controls and CFS patients, and a third parameter, serum vitamin B_{12}, was higher in the TMJ-CFS compared with the control subjects (Table 2). The discriminant function analysis comparing the blood biochemistry profiles between the controls, CFS and TMJ-CFS groups indicated that these three groups had different biochemistry profiles ($P < .002$), where methaemoglobin was again, the primary discriminant variable. Figure 2 shows the extremely efficient separation of control, CFS and TMJ-CFS subjects in the canonical scatter plot generated by the discriminant function analysis.

FIGURE 2. Canonical scatter plot of the variation in the measured red blood cell and oxidative markers in the control subjects and the CFS patients with and without TMJ clicking and/or locking.



Associations of Biochemical Features with Hematological Parameters

Methaemoglobin was the primary variable that differentiated FP-CFS from the control and CFS groups and in addition, ferritin and malondialdehyde were elevated in the FP-CFS group. These variables were therefore further investigated for associations with changes in the hematological parameters measured in the study, using regression analyses (summarised in Table 3). In the FP-CFS group, methaemoglobin was positively associated with vitamin B_{12}, whilst in the CFS group, methaemoglobin was negatively correlated with levels of vitamin B_{12}. Multiple regression analyses of methaemoglobin concentration against the other blood parameters showed that changes in this variable had strong effects on the blood parameter profile and the primary correlate was vitamin B_{12}. The data for ferritin and malondialdehyde also show that there were differences in correlations between the control, CFS and

TABLE 3. Associations between haematology measurements and those parameters (methaemoglobin, ferritin and malondialdehyde) that were elevated in CFS patients reporting face pain.

METHAEMOGLOBIN (MetHb)	**Control** *n = 27*		**CFS** *n = 16*		**FP-CFS** *n = 17*	
Spearman Rank correlations	r	*P*	r	*P*	r	*P*
% Saturation		NS	−.68	< .05		NS
Vitamin B_{12}		NS	−.88	< .001	.60	< .02
Total iron binding capacity		NS	.82	< .007		NS
Multiple Regression Analyses						
Control	**CFS**				**FP-CFS**	
R^2 = .792, F = 5.98, P < .005	R^2 = .999, F = 30752, P < .005				R^2 = .997, F = 29.79, P< .14	
Variables	**Variables**				**Variables**	
(1) Ferritin (+)	(1) Vit B_{12} (−)				(1) Vit B_{12} (+)	
(2) 2,3-DPG (+)	(2) RBC Folate (+)				(2) Haemoglobin (−)	
(3) Vit B_{12} (−)	(3) 2,3-DPG (+)				(3) Malondialdehyde (+)	
FERRITIN	**Control**		**CFS**		**FP-CFS**	
Spearman Rank correlations	r	*P*	r	*P*	r	*P*
WBV(LSR)	.64	< .002		NS		NS
Haemoglobin		NS		NS	.59	< .02
WBV(HSR)		NS	.68	< .05		NS
Total iron binding capacity		NS	−.83	< .006		NS
Erythrocyte distribution width	−.51	< .03		NS		NS
Multiple Regression Analyses						
Control	**CFS**				**FP-CFS**	
R^2 = .703, F = 6.17, P < .004	R^2 = .999, F = 4634, P< .02				R^2 = .949, F = 7.49, P < .04	
Variables	**Variables**				**Variables**	
(1) WBV(LSR) (+)	(1) RDW (−)				(1) Haemoglobin (+)	
(2) TIBC (−)	(2) 2,3-DPG (−)				(2) Haematocrit (−)	
(3) Malondialdehyde (−)	(3) Malondialdehyde (−)				(3) Malondialdehyde (+)	
MALONDIALDEHYDE (MDA)	**Control**		**CFS**		**FP-CFS**	
Spearman Rank correlations	r	*P*	r	*P*	r	*P*
2,3-Diphosphoglycerate	.46	< .05		NS		NS
MCV	−.63	< .003		NS		NS
Multiple Regression Analyses						
Control			**CFS**		**FP-CFS**	
R^2 = .866, F = 12.87, P < 0.001			R^2 = .999, F = 7390, P< .009		R^2 = .989, F = 14.81, P< .06	
Variables			**Variables**		**Variables**	
(1) MCV (−)			(1) MCV (−)		(1) Methaemoglobin (+)	
(2) TIBC (−)			(2) 2,3-DPG (−)		(2) Ferritin (+)	
(3) GSH (−)			(3) WBV(LSR) (−)		(3) ESR (−)	

Abbreviations: MCV = mean corpuscular haemoglobin, TIBC = total iron binding capacity, GSH = glutathione, 2,3-DPG = 2,3-diphosphoglycerate, WBV(LSR) = whole blood viscosity (low shear rate), WBV (HSR) = whole blood viscosity (high shear rate), ESR = erythrocyte sedimentation rate; RDW = red cell distribution width.

FP-CFS groups indicating different homeostasis in each of these groups. The multivariate analyses also show that changes in concentration of either ferritin or malondialdehyde were strongly associated with changes in the blood parameter profile. In addition, the changes in correlation profile were different for the separate groups, where for example, the primary correlates for ferritin concentrations in the control, CFS and FP-CFS groups were WBV(LSR), RDW and haemoglobin respectively. These data provide evidence of altered and characteristic homeostasis associated with different symptom profiles.

Methaemoglobin was also the primary variable that differentiated TMJ-CFS from the control and CFS groups and in addition, malondialdehyde, vitamin B_{12} and ferritin were identified as differential parameters in the TMJP-CFS group. These variables were therefore further investigated for associations with changes in the hematological parameters measured in the study, using regression analyses (summarised in Table 4). In the TMJ-CFS group, methaemoglobin was positively associated with glutathione, whilst in the CFS group, methaemoglobin was positively correlated with levels of malondialdehyde. Multiple regression analyses of methaemoglobin concentration against the other blood parameters in the TMJ-CFS revealed that changes in this variable had strong effects on the blood parameter profile ($R^2 = .99$, $P < .02$), and the primary correlate was glutathione. The data for ferritin, malondialdehyde and vitamin B_{12} also show that there were differences in correlations between the control, CFS and TMJ-CFS groups indicating different homeostasis in each of these groups. The multivariate analyses also show that changes in concentration of ferritin, malondialdehyde or vitamin B_{12} were strongly associated with changes in the blood parameter profile. In addition, the changes in correlation profile were different for the separate groups, where for example, the primary correlates for ferritin concentration for the control, CFS and P-CFS groups were WBV(LSR), RDW and WBV(HSR), respectively. These data again provide evidence of altered and characteristic homeostasis associated with different symptom profiles.

These data indicate that the normal association between markers of oxidative metabolism is deregulated in the CFS cohort and variations in

TABLE 4. Associations between haematology measurements and those parameters (methaemoglobin, ferritin and malondialdehyde) that were elevated in CFS patients reporting TMJ clicking/locking.

METHAEMOGLOBIN (MetHb)	**Control** *n = 27*		**CFS** *n = 20*		**TMJ-CFS** *n =12*	
Spearman rank correlations	r	*P*	r	*P*	r	*P*
Glutathione		NS		NS	.79	< .02
MDA		NS	.60	< .02		NS
Multiple Regression Analyses						
Control	**CFS**			**TMJ-CFS**		
R^2 = .792, F = 5.977, P< .005	R^2 = .679, F = 5.285, P< .02			R^2 = .999, F = 3856, P< .02		
Variables	**Variables**			**Variables**		
(1) Ferritin (+)	(1) Malondialdehyde (+)			(1) GSH (+)		
(2) 2,3-DPG (+)	(2) Ferritin (+)			(2) RDW (−)		
(3) Vit B_{12} (−)	(3) TIBC (+)			(3) Malondialdehyde (+)		
FERRITIN	**Control**		**CFS**		**TMJ-CFS**	
Spearman rank correlations	r	*P*	r	*P*	r	*P*
WBV(LSR)	.64	< .002		NS		NS
WBV(HSR)		NS		NS	.79	< .02
Haemoglobin		NS		NS	.72	< .02
Total iron binding capacity	−.51	< .03	−.52	< .05		NS
Red cell distribution width		NS	−.54	< .04		NS
Multiple Regression Analyses						
Control	**CFS**			**TMJ-CFS**		
R^2 = .703, F = 6.168, P< .004	R^2 = .884, F = 7.585, P < .008			R^2 = .999, F = 4423, P< .02		
Variables	**Variables**			**Variables**		
(1) WBV(LSR) (+)	(1) RDW (−)			(1) WBV(HSR) (+)		
(2) TIBC (−)	(2) Methaemoglobin (+)			(2) WBV(LSR) (−)		
(3) Malondialdehyde (−)	(3) TIBC (−)			(3) Haemoglobin (+)		
MALONDIALDEHYDE (MDA)	**Control**		**CFS**		**TMJ-CFS**	
Spearman rank correlations	r	*P*	r	*P*	r	*P*
Methaemoglobin		NS	.60	< .02		NS
2,3-Diphosphoglycerate	.46	< .05		NS		NS
Erythrocyte sedimentation rate		NS		NS	−.69	< .05
MCV	−.63	< .003		NS		NS

MALONDIALDEHYDE (MDA)	**Control**	**CFS**	**TMJ-CFS**
Multiple Regression Analyses			
Control	**CFS**	**TMJ-CFS**	
R^2 = .866, F = 12.87, P< .001	R^2 = .928, F = 12.82, P<. 002	R^2 = 0.999, F = 2671000, P < .001	
Variables	**Variables**	**Variables**	
(1) MCV (−)	(1) Methaemoglobin (+)	(1) ESR (−)	
(2) TIBC (−)	(2) MCV (−)	(2) WCC (+)	
(3) GSH (−)	(3) WCC (−)	(3) Ferritin (−)	

VITAMIN B_{12}	**Control**		**CFS**		**TMJ-CFS**	
Spearman rank correlations	r	*P*	r	*P*	r	*P*
2,3-Diphosphoglycerate	.48	< .04	.51	< .05	−.89	NS
Total iron binding capacity		NS		NS		< .001
Multiple Regression Analyses						
Control	**CFS**			**TMJ-CFS**		
R^2 = .821, F = 5.724, P< .007	R^2 = .902, F = 9.240, P<. 005			R^2 = .999, F = 6636, P< .01		
Variables	**Variables**			**Variables**		
(1) 2,3-DPG (+)	(1) 2,3-DPG (+)			(1) TIBC (−)		
(2) GSH (+)	(2) RBC Folate (+)			(2) CRP (−)		
(3) WBV(LSR) (+)	(3) TIBC (−)			(3) WBV(HSR) (−)		

Abbreviations: MCV = mean corpuscular haemoglobin, TIBC = total iron binding capacity, GSH = glutathione, 2,3-DPG = 2,3-diphosphoglycerate, WBV(LSR) = whole blood viscosity (low shear rate), WBV (HSR) = whole blood viscosity (high shear rate), ESR = erythrocyte sedimentation rate, RDW = red cell distribution width.

these associations between certain oxidative parameters are associated with variation in TMD symptom expression.

DISCUSSION

This study found that the self-reported TMD symptoms of face pain and TMJ clicking and/or locking in the CFS patients were associated with increases in erythrocyte methaemoglobin, malondialdehyde, ferritin and vitamin B_{12} compared with controls (Table 2). Multiple regression analysis revealed that methemoglobin was the principle discriminating factor determining TMD symptom expression in the CFS patients (Table 2). These data indicated that increases in methaemoglobin and the

other oxygen radical induced changes were associated with TMD symptom expression in CFS patients. The study also found that CFS patients with TMD symptoms, particularly those with TMJ clicking and/or locking, could be differentiated from both controls and the remaining CFS patients using their blood parameters. This suggests that TMD symptom expression is associated with deregulation of normal biochemistry, which supports that contention that TMD may be a group of distinct clinical entities with their own characteristic biochemistry changes (3).

Methemoglobin is a product of the oxidation of the ferrous iron of the haem group of the haemoglobin molecule (12) the formation of which is controlled by NADH-methemoglobin reductase (13). Nitric oxide (14), bacterial toxins (15) and many drugs (16) can induce methemoglobin formation. Normally the haemoglobin molecule and the membrane of the erythrocyte are protected by the reducing systems within the erythrocyte. It is generally considered that under situations of oxidative stress, the protective antioxidant systems are altered (17) with a concomitant rise in the products of oxidation. The data from the present study suggest that deregulation of the intracellular redox status was involved in TMD symptom expression. Our group has reported that jaw muscle pain (Research diagnostic criteria/Temporomandibular dysfunction type 1a/Myofascial pain) (18) was associated with an increase in the membrane damaging toxin production by coagulase negative *Staphylococcus* (19). It was therefore of interest to note that increases in TMD symptom severity were associated with alterations in ferritin, C-reactive protein and the ESR suggesting an inflammatory based reaction to the pathogen(s) may be involved. This also supports our groups' observation that TMD symptoms are associated with increases in infectious events at onset (4).

We have demonstrated a strong statistical association between certain markers of oxidative damage to erythrocytes and TMD symptoms in CFS patients and an ability to form two homogeneous groups within the CFS patient cohort using TMD symptoms and red blood oxidative markers. Methemoglobin was found to be the major indicator, of those assessed, of TMD symptom expression whilst increases in the markers suggestive of pathogen-associated changes, C-reactive protein, ferritin

and ESR were also found to be associated with TMD symptom severity. These changes suggest that free radical formation is a contributor to TMD symptom expression in a distinct subgroup of CFS patients and that long-term chronic illness may be reflected in increased oxidative damage within the host leading to increased symptom expression.

These data also support the hypothesis that although CFS patients may have an infectious etiology (20-23), they may also have more frequent non-etiologically pathogen-related problems than in the normal population. This is suggestive that a HIV-like model may be more appropriate for these patients than a single infective onset model (20-23) or a neuropsychiatric model as proposed by other researchers (24-27). A potentially pathogen-associated condition such as TMD (19) has an increased prevalence in CFS patients compared with in the normal population (3) as seen in this paper and other published research (28-29) which is not unlike that seen in HIV. The data in this paper support the contention that secondary or opportunistic infections or other pathogen-related conditions may make a significant contribution to the over all morbidity of CFS patients. This also offers an explanation for the failure to find a common pathogen with CFS patients where a number of different yet common pathogens may contribute to symptoms expression within a susceptible immune compromised patient.

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