

Prevalence of Abnormal Cardiac Wall Motion in the Cardiomyopathy Associated with Incomplete Multiplication of Epstein-Barr Virus and/or Cytomegalovirus in Patients with Chronic Fatigue Syndrome*

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Abstract. We reported unique incomplete herpesvirus (Epstein-Barr Virus (EBV) and/or nonstructural (HCMV) cytomegalovirus) multiplication in 2 distinct subsets of CFS patients. The CFS subsets were identified by: a) presence of IgM serum antibodies to HCMV nonstructural gene products p52 and CM₂ (UL44 and UL57), and/or b) IgM serum antibodies to Epstein-Barr virus viral capsid antigen (EBV, VCA IgM). Diagnostic IgM serum antibodies were found in two independent blinded studies involving 49 CFS patients, but the same antibodies were absent in 170 control patients ($p < 0.05$). Abnormal 24 Hr-electrocardiographic monitoring, tachycardias at rest and, in severe chronic cases, abnormal cardiac wall motion (ACWM) were seen in these same CFS patients. We now report a prospective consecutive case control study from 1987-1999 of cardiac dynamics as measured by radionuclide ventriculography in 98 CFS patients from 1987-1999. Controls were patients with various

malignancies who were evaluated in protocols requiring radionuclide ventriculography before initiation of cardiotoxic chemotherapeutic agents. The prevalence of abnormal cardiac wall motion (ACWM) at rest in CFS patients was 10 out of 87 patients (11.5%). With stress exercise, 21 patients (24.1%) demonstrated ACWM. Cardiac biopsies in 3 of these CFS patients with ACWM showed a cardiomyopathy. Among the controls, ACWM at rest was present in 4 out of 191 patients (2%) ($p = 0.0018$). A progressive cardiomyopathy caused by incomplete virus multiplication of EBV and/or HCMV in CFS patients is present.

The clinical illness described as chronic fatigue syndrome (CFS) suggests a prolonged viral infection, but no single virus has been identified. A subset classification of patients with CFS may be required to design successful blinded clinical trials of antiviral therapy (1,2). However, in previous trials subset classification of CFS patients has not been utilized, and therapeutic interventions have not been useful (3). With subset classification, one open preliminary trial of antiviral therapy (valacyclovir) in a cohort of CFS patients with single virus Epstein-Barr Virus (EBV) persistent infection is promising (4). In this open trial, CFS patients with single virus EBV infections were benefitted by valacyclovir as prescribed, but CFS patients treated with valacyclovir who had co-infections with cytomegalovirus (HCMV) did not improve ($p < 0.05$). Valacyclovir has significant anti-EBV antiviral activity (IC₅₀ equals 4.4-13.3 μm), but does not have

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significant anti-HCMV activity and, thus, the non-beneficial response to valacyclovir in CFS patients with EBV-HCMV co-infections is reasonable.

In the first CFS reported subset, there were 16 CFS patients with human HCMV IgM p52 and CM₂ serum antibodies to the viral tegument gene products encoding for the HCMV ICP36 protein family and the major DNA-binding protein (1). The p52 and CM₂ antigens are gene products of UL44 and UL57 of the HCMV genome. Other CFS patients (18 patients) with HCMV(V) IgG antibodies, non-fatigued HCMV(V) IgG-positive control patients (18 patients), random HCMV(V) IgG-positive control patients from a clinical laboratory (26 patients) and non-fatigued HCMV(V) IgG-negative control patients did not have HCMV, IgM p52 or CM₂ serum antibodies ($p < 0.05$). Thus, 77 various control patients did not have IgM p52 or CM₂ serum antibodies. All patients in this initial study had no conventional IgM serum antibodies to HCMV(V) and, therefore, would classically be interpreted as showing no serologic evidence of HCMV current infection. The presence of HCMV IgM serum antibodies to gene products p52 and CM₂ (UL 44 and UL 57) detected incomplete HCMV multiplication in which a part of the HCMV protein-coding content of the HCMV genome is processed, but remains unassembled. These findings suggested that the presence of IgM HCMV serum antibodies to p52 and/or CM₂ is an etiologic diagnostic test in this subset of CFS patients (1). A second CFS subset was next identified in 33 CFS patients who were shown to have positive IgM serum antibodies to Epstein-Barr Virus viral capsid antigen (EBV VCA), and these serum antibodies persisted in the serum of these CFS patients for 24-42 months. The EBV VCA IgM serum antibodies were not present in 93 control patients ($p < 0.0001$). To be sure, EBV infectious mononucleosis EBV VCA IgM serum antibodies are uniformly absent within 6 months (2). Incomplete EBV and/or HCMV multiplication may be an important pathogenetic mechanism in the understanding of the disease-cause in CFS.

Concurrent studies have been directed to the heart of CFS patients as a possible site of incomplete herpesvirus multiplication. We confirmed a usually normal resting electrocardiograms in CFS patients (5,6), but we, unexpectedly, found repetitively abnormal inverted to isoelectric T-waves at 24-Hr electrocardiographic recordings (Holter monitor) in 24 CFS patients. The mean age of these CFS patients was 36 years, and the abnormal Holter recordings were present in all (100%) of the CFS patients. Similar abnormal Holter findings were present in 22.4% of 116 control patients whose mean age was 38 years ($p < 0.01$). Resting left ventricular ejection fractions were normal in CFS patients, but 8 of the 24 CFS patients demonstrated abnormal cardiac wall motion (ACWM) at exercise stress (stress multiple gated acquisition (MUGA) tests (7). The 24-Hr

ECG recordings were repeated in a second random double-blinded investigation with uninvolved blinded cardiologist physician readers of the blinded tracings. Again, abnormal oscillating T-waves at Holter monitoring were found in 67 consecutive CFS patients. These latter CFS patients were matched for age, place, time and absence of confounding medical diseases with 78 non-CFS patients. A prevalence of labile T-wave abnormalities by Holter monitoring was again greater in CFS patients than in non-CFS patients ($p < 0.01$). The absence of abnormal T-waves at Holter monitoring made the diagnosis of CFS unlikely (statistical sensitivity, 0.96). Abnormal cardiac wall dynamics were then described in detail in 11 CFS patients, and right ventricular endomyocardial biopsies showed a cardiomyopathy at light and electron microscopic study (8-9).

Other investigators have similarly found physiological changes in CFS patients which may have been a result of cardiac dysfunction. Among these abnormalities are hypotensive responses with tilt-table tests, tachycardias at rest, diminished erythrocyte circulating blood volumes with normal plasma volumes, and reduced left ventricular end systolic and diastolic dimensions. Abnormal impedance cardiography, with thin posterior left ventricular walls and decreased left ventricular masses, as well as gravitational venous pooling and decreases in oxy-Hb upon standing, are reported (10-17). Symptoms in CFS patients which may be related to these circulatory abnormalities are light-headedness, visual blurring, palpitations and weakness upon assuming upright postures. Activities of normal life and any exercise accentuates these life-altering symptoms. Severe CFS predicts a lower cardiac output ($R^2 = 0.46$, $p < 0.0002$) (18).

The prevalence of ACWM in CFS has not been known (19). We present a case control study of cardiac dynamics in 98 random CFS patients and 191 consecutive cancer patients who are a control group. No known cardiac disease was present in CFS or control patients.

Materials and Methods

Prevalence of abnormal cardiac wall motion in CFS patients. From January 1, 1987 through December 31, 1994, ninety-eight CFS patients were seen at a single center in a consecutive case series. CFS patients met defined criteria (5-6) and had abnormal Holter monitoring (7-8). Patient histories, physical examinations and follow-up care was done. Standard 12-lead resting ECG, 24-Hr Holter monitor (Applied Cardiac Systems, Laguna Hills, CA 92653-1332, USA), 2-D echocardiogram, rest/stress myocardial perfusion study (thallium 201 or TC-99m sestamibi), and MUGA rest/stress radionuclide ventriculography (RVG) examinations were performed (7). Using radioisotopic-gated blood pool methods radionuclide ventriculography (RVG) studies were possible in 87 of 98 CFS patients. These methods are reported (9). At rest and exercise, left ventricular ejection (EF), left ventricular blood pool area, and left ventricular wall motion were examined. A normal resting ejection fraction (EF) in our laboratory is $\geq 55\%$. A normal

Table I. Demographic characteristics in 98 chronic fatigue syndrome patients in Birmingham, Michigan 1987 – 1994.

Variable	All CFS Patients*	CFS Patients with abnormal stress MUGAs (21)	CFS Patients with Normal stress MUGAs (66)	Significance
Age, years, mean	42.3±10.6	45.2±11.0	41.6±9.5	NS ⁺
Women %	87%	81%	91%	NS
Duration of CFS (months)	12.2±11.3 (80)	9.6±6.3 (15)	12.6±11.1 (65)	NS
Other medical diagnoses %	21%	32%	15%	NS
Diabetes mellitus %	0%			NS
Hypertensive vascular disease %	3%	0%	4%	NS
Total cholesterol > 250 mg%	12%	19%	8%	NS
Obesity %	6%	6%	8%	NS
Cigarette smokers	16%	20%	13%	NS
Alcohol %				
1. Non-user	43%	40%	44%	NS
2. 1 or 2/mos **	37%	45%	36%	
3. 1 or 2/wk	12%	5%	13%	
4. 1 or 2/day	7%	5%	7%	
5. 3+/day	1%	5%	0%	
Antidepressants at first visit	11%	0%	15%	NS

*The number of CFS patients evaluated is listed in parenthesis.

**One jigger equals 45cc alcoholic beverage

⁺NS, not significant

response to maximum stress is $\geq 5\%$ EF units above the rest EF. Abnormal responses to RVG studies were identified in routine readings without knowledge of the patient or of the ongoing investigation. Peak exercise, rate/pressure product and mean kilonmeter values achieved were calculated.

In several CFS patients in whom ACWM was identified, right ventricular endomyocardial biopsies were taken and immediately placed in 25% cacodylate buffered glutaraldehyde, post-fixed in 10% osmium tetroxide and embedded in Epon 812. Ten serial 1 μ m thick sections were obtained from each block, stained with toluidine blue, and examined by light microscopy. Specimens were examined for cellular infiltration, myofiber hypertrophy, myofiber disarray, interstitial fibrosis, perimysial fat infiltration, myofiber necrosis, amount of mitochondria, fat droplets and lipofuscin granules. Cardiac biopsies with cellular infiltrates were read as myocarditis. Other pathologic changes, but without a cellular infiltrate, were interpreted as cardiomyopathy.

Controls. Resting RVGs are done at WBH in cancer patients before use of chemotherapeutic agents with possible cardiac toxicity. From 1987-1999, all pre-chemotherapy RVGs in 191 consecutive cancer patients ≤ 55 years old were reviewed. Cancer patients who had previous coronary artery disease, chest pain, arrhythmias, chronic lung disease, or renal failure were excluded from the control group. These exclusions were done to exclude patients from the control group with known cardiac disease. By "definition" CFS patients do not have cardiac disease (5,6). Hospital records of patients in the control group were reviewed. If the cancer patient had hypertension or diabetes mellitus which was well controlled, this patient was included in the control group. If a criterion for exclusion was found, this patient was excluded from the control group. If hospital records were unavailable for review, this patient was included in the control group. Breast cancer was the most common malignancy.

Statistics. CFS patients with abnormal stress MUGAs were compared with CFS patients with normal stress MUGAs. Dichotomous variables (normal variable with two categories, *e.g.*, abnormal/normal and yes/no) were evaluated by Fisher's exact test. Differences in alcohol use were evaluated by Chi-square analysis. For continuous variables (variables measured on an interval scale, differences between the two patient groups were examined using *t*-tests. Using an unpaired *t*-test (two-tailed test, $p=0.05$), the ages and the mean left ventricular ejection fraction of CFS and cancer patients both groups of patients who were under the age of 55 years old were compared. The ages of the patients with abnormal MUGA studies were compared using an unpaired *t*-test (two-tailed test, $p=0.05$). Gender frequencies and other abnormal frequencies were examined by Fisher's exact test (two-tailed test, $p=0.05$).

Results

Demographic characteristics in CFS. The mean age of the 98 CFS patients was 42.3±10.6 years (Table I). Eighty-seven percent (87%) were women. The duration of their CFS was 12.2±11.3 months. Other medical diagnoses were few. There was hypercholesterolemia (12%), obesity (6%), and hypertensive vascular disease (3%). No CFS patient had diabetes mellitus. Sixteen percent (16%) of CFS patients smoked cigarettes. Fifty-seven percent (57%) drank alcohol at least occasionally. One percent (1%) had 3+ drinks per day. Prior to diagnosis of CFS, none had psychiatric disease. After the onset of CFS, reactive depressions were present in 11%. Abnormal left ventricular dynamics were observed in 11.6% of the CFS patients at rest, and in 24.1% of the 87 CFS patients who underwent stress RVG (Table II).

Table II. *Cardiologic tests in 98 chronic fatigue syndrome patients in Birmingham, Michigan, 1987-1994.*

Variable	All CFS patients	CFS patients with abnormal stress MUGAs	CFS patients with normal stress MUGAs	Significance
Abnormal ECG%	31% (98)*	33% (21)	29% (66)	NS**
Oscillating abnormal T-waves at Holter monitoring	100% (98)	100% (21)	100% (66)	NS
Mitral valve prolapse	22% 87%	33% (21)	20% (56)	NS
Abnormal 2-D echocardiogram %	5% (83)	20% (20)	0% (53)	<i>p</i> =0.018
Abnormal stress myocardial perfusion study (thallium 201 or TC-909 sestamibi)	2% (44)	9.1% (11)	0% (33)	NS
Abnormal MUGA rest/stress study	24.1% (87)	- -	- -	- -
Mean ejection fraction, rest	61.3±6.8% (87)	58.0±6.9% (21)	62.6±6.5% (66)	<i>p</i> =0.007
Mean ejection fraction, stress	70.8±8.8% (86)	64.0±10.2 (21)	73.4±7.3 (21)	<i>p</i> <0.001
Abnormal wall motion, rest	11.6% (87)	48% (21)	0% (66)	<i>p</i> =0.003
Abnormal wall motion, stress	4.6% (86)	19% (21)	0% (65)	<i>p</i> =0.003
Ventricular dilatation, rest	6.9% (87)	29% (21)	0% (66)	<i>p</i> <0.001
Ventricular dilatation, stress	4.6% (86)	19% (21)	0% (65)	<i>p</i> =0.003
Peak pressure product, mean	224.1±55.1 (84)	236.2±54.4 (20)	222.7±55.7 (64)	NS
Kiloponimeters, achieved, mean	566.8±199.6 (84)	580.0±201.6 (20)	592.2±194.6 (64)	NS

*The number of CFS patients evaluated is listed in parenthesis

**NS, not significant

Demographic findings in CFS patients with abnormal left ventricular dynamics (21 patients) and those with normal left ventricular dynamics (66 patients) were similar (Table I).

Cardiac tests. Standard resting 12-lead ECGs were normal in 69% of the CFS patients. In the others, isolated nonspecific T-wave flattening or T-wave inversion, usually in standard leads I or III or occasionally in both leads I and III, were abnormal findings (Table II). Precordial lead ECGs were normal. Oscillating intermittent, repetitive abnormal T-wave flattening and T-wave inversions at 24-Hr. ECG Holter monitoring were present in all 98 patients. The 66 CFS patients with normal responses to stress MUGA studies had normal 2-D echocardiograms, except for the cohort with mitral valve prolapse (20%). Four CFS patients with ACWM on RVG demonstrated abnormal resting echocardiograms. The patients with abnormal left ventricular dynamics and abnormal echocardiograms included three women, ages 18, 45, and 49 years; and one was a 58-year-old man. In two of these patients, there was a global left ventricular dilatation. Infero-basilar hypokinesis was seen in one patient, and left atrial dilation in another patient. In the two designated groups of CFS patients, resting 2-D echocardiograms were also different (*p*=0.018).

To exclude co-existing ischemic cardiomyopathy, forty-four (44) CFS patients underwent stress myocardial perfusion studies (thallium201 or TC-99m sestamibi). In 43 of these 44 CFS patients, studies were normal. In the single patient with a positive myocardial perfusion study, the coronary angiogram was normal.

Table III. *Abnormal cardiac wall motion at rest by MUGA studies in CFS and control patients.*

	CFS patients (87)*	Control patients (191)	Significance
Age, years, mean	42.3±10.6	48.9±9.1	<0.001
Women %, entire cohort	87%	74%	0.0178
Mean ejection fraction, rest	61.3±6.8%	63.3±7.1%	0.0278
Percent, ACWM	11.6% (10 patients)	2.0% (4 patients)	0.0018

*Number in parenthesis is the number of patients in the group.

Twenty-one of 87 CFS patients (24.1%) had abnormal responses to rest/stress MUGA studies (ACWM). Repeated RVG comparisons between CFS patients with and without abnormal cardiac wall motion at MUGA study demonstrated decreased left ventricular function in patients with abnormal MUGAs (Table II). Mean resting Ejection Fraction (EF), rest (58.0±6.9% versus 62.6±6.5% (*p*=0.007); mean EF, stress 64.0±10.2% versus 73.4±7.3% (*p*≤0.001); abnormal wall motion, rest (10 patients, *p*=0.003); abnormal wall motion, stress (4 patients, *p*=0.003); ventricular dilatation, rest (6 patients, *p*≤0.001) and ventricular dilatation, stress (4 patients, *p*=0.003) describes this CFS cohort. Peak pressure products and kiloponimeters achieved were similar

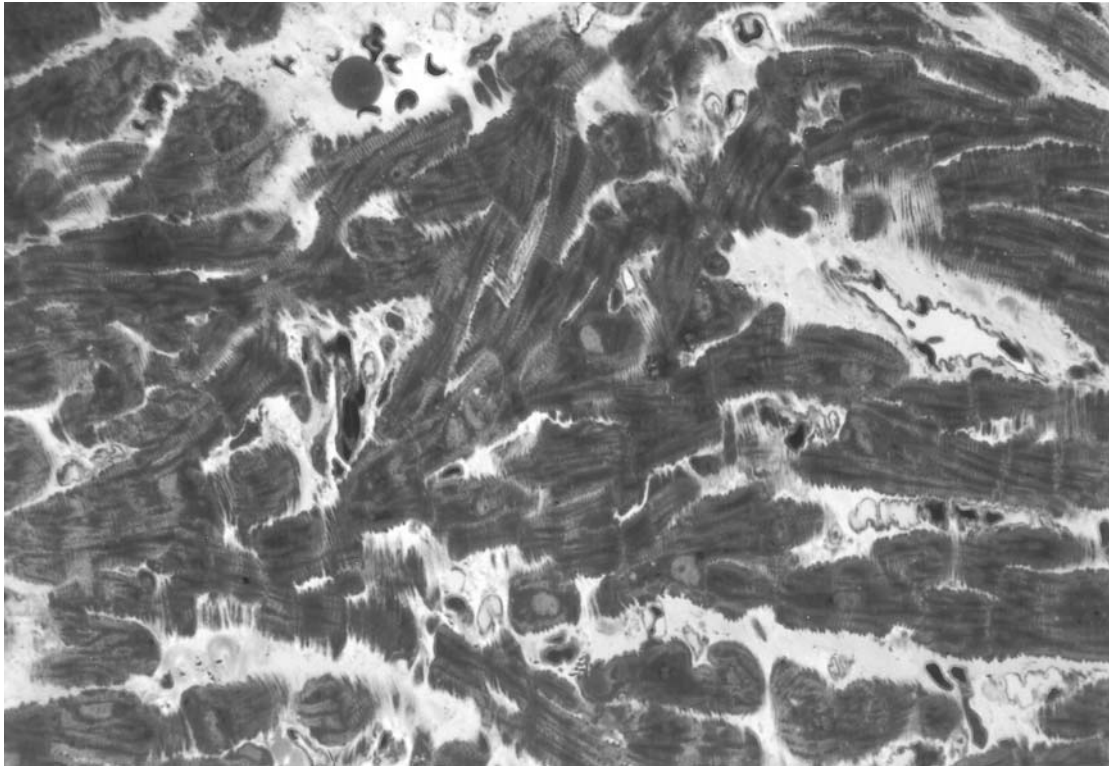


Figure 1a. *This cardiac section from a 30-year-old woman shows myofiber disarray with no cellular infiltrate (case no. 1, toluidine blue, x 400).*

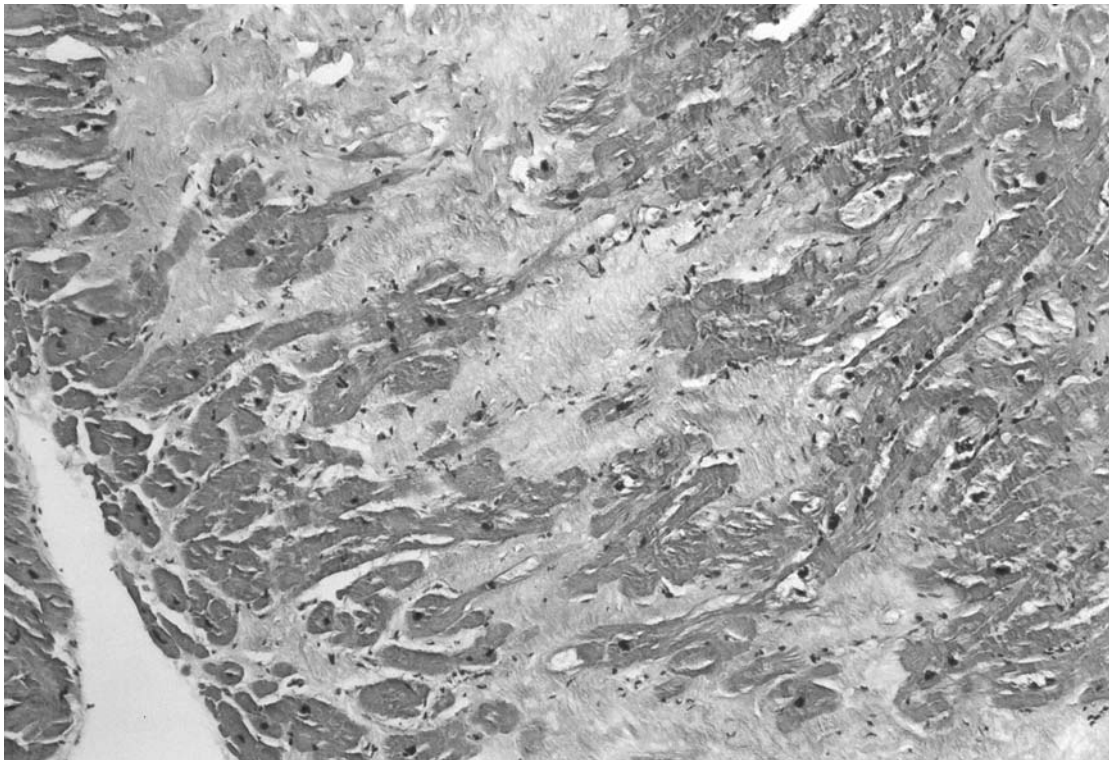


Figure 1b. *This cardiac section from a 40-year-old woman demonstrates focal interstitial fibrosis and myofiber hypertrophy (case no. 2, hematoxylin eosin, 10 x 1.25).*

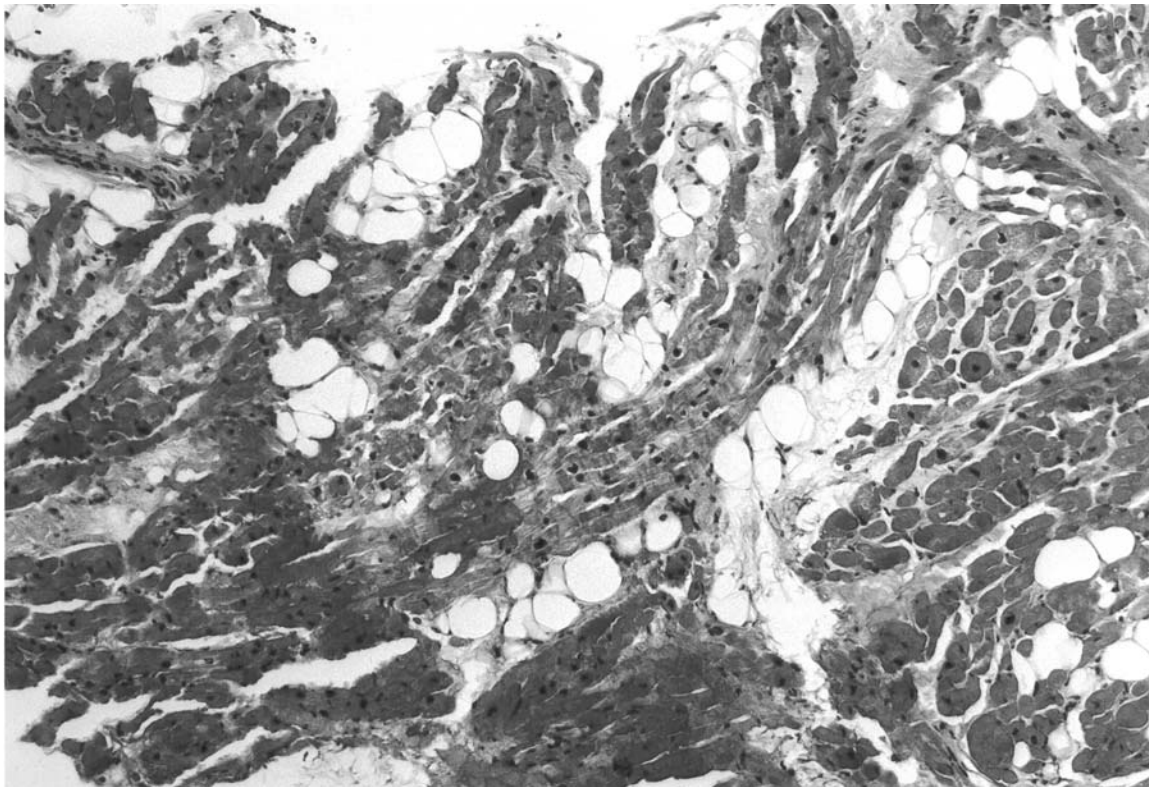


Figure 1c. This cardiac section from a 43-year-old woman demonstrates fatty infiltration replacing myocytes. There is also spotty fibrosis (case no. 3, hematoxylin eosin, 10 x 1.25).

in CFS patients with and in those without abnormal cardiac dynamics. In three CFS patients, left ventricular ejection fractions of 40%, 45% and 46% (normal, > 55%) were present. Thus, the two cohorts of CFS patients who were divided on the basis of normal cardiac wall motion, or ACWM were also statistically different in both rest and stress EFs and ventricular dilatation.

MUGA rest RVG studies in controls (Table III). The mean age of the 191 control patients was 48.9 + 9.1 years, while CFS patients were 42.3±10.6 years ($p<0.001$). Like CFS patients, control patients were mostly women (CFS patients, 87%; controls, 74%, $p= 0.0178$). The mean resting EF of the control patients was 63.3±7.1% while the mean resting EF of CFS patients was 61.3±6.8% ($p=0.028$). Four of the 191 (2%) control patients had ACWM at rest, while 10 of the 87 (11.6%) CFS patients had ACWM ($p=0.0018$). Control patients, were older, but had higher resting EFs and less ACWM.

Cardiac biopsies (Figure 1). Cardiac biopsies from CFS patients, a) 30-year-old, b) 40-year-old and c) 43-year-old

woman with ACWM are shown. Cardiac muscle disarray, cardiac fibrosis and fatty infiltration replacing cardiac myofibers are evident. There is no cellular infiltrate of myocarditis (17-20).

Discussion

The present report describes the prevalence of cardiomyopathy in CFS patients. One outcome of incomplete HCMV and/or EBV multiplication may be this cardiomyopathy. These findings are interesting because: 1) cardiac dysfunction in the pathologic physiology of CFS has been controversial (5,6,19); 2) a pathologic result from incomplete virus multiplication has not been reported; 3) a pathologic role for herpesviruses in CFS patients is considered remote (20) and 4) the infectious cause of any cardiomyopathy is uncertain (21). Finally, the importance of 5) the present and earlier reports in the design of parameters for subset analysis of CFS patients in the evaluations of antiviral therapy in CFS patients in random double-blinded controlled clinical trials is evident.

Chronic fatigue syndrome is epidemic in young women in the US, approaching the occurrence of diabetes mellitus (522 CFS women, and 249 CFS men per 100,00 US population) (22). If the present data are confirmed by others, they may meet the definition of Gunther Stent's "premature scientific discovery" (23). Premature scientific discoveries are met by the scientific community with resistance and ridicule (24). The present data are part(s) in a series of observations which, however, appear to fit together in a continuing reasonable sequence. Certainly, a healthy population of young adults who are predominantly women would, if possible, have been a better group of control patients here, but the control patients with recently discovered mostly breast cancers "seem" adequate. Control patients are a decade older than the CFS patients and, therefore, would be expected to have a "higher" (not lower) occurrence of ACWM. On the contrary, CFS patients have an increased occurrence of ACWM at MUGA study by an order of "five" compared to controls ($p=0.0018$). To be sure, ACWM may be equally well or better studied by other cardiologic methods including, for instance, stress echocardiography. Nevertheless, the validity of ACWM in severe CFS appears clear.

The CFS cardiomyopathy presents as a resting tachycardia, often with a positive tilt table test (10-11), with abnormal oscillating T-wave flattening and T-wave inversions at 24 Hr. ECG Holter monitoring (7-8). In severe CFS cases, ACWM, stress and then rest and, finally, with a decreased left ventricular ejection fraction follows (9). The current definition of cardiomyopathy may include only the later stages of a worsening pathology with a progressive earlier undetected phase. Only when ACWM with/without a decreased left ventricular ejection fraction and with no coronary artery disease and no valvular cardiac disease is a cardiomyopathy recognized. Patients with CFS have ACWM in 11.6% of the cases at rest compared to 2% of the controls. With exercise stress CFS patients demonstrate ACWM in 24.1% of cases. Abnormal cardiac wall motion at rest indicates severe cardiac dysfunction. (25) Abnormal cardiac wall motion at rest is present in patients with coronary artery disease, hibernating myocardium or acute myocarditis (26-28).

An etiologic role for incomplete herpesvirus multiplication in CFS requires confirmation. It may be, however, that the many immunologic abnormalities documented in CFS patients are associated host-defense responses to incomplete herpesvirus multiplication (29). Different from virus myocarditis, the herpesvirus genome (EBV and HCMV) is not present in the CFS patient's myocardium as tested by polymerase chain reaction (30,31). A more appropriate test with cardiac tissues from CFS patients may be an attempt to identify the specific viral gene fragments inducing IgM serum antibodies to HCMV p52 and/or HCMV CM₂ and/or serum

antibodies to EBV viral capsid IgM antigen. We need add a cautionary note. Three patients with CFS cardiomyopathy in our series had severe post-biopsy bleedings. Fortunately, none of these patients died. The affected myocardium in CFS cardiomyopathy may be especially friable.

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