



Allostatic load is associated with symptoms in chronic fatigue syndrome patients

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Objectives: To further explore the relationship between chronic fatigue syndrome (CFS) and allostatic load (AL), we conducted a computational analysis involving 43 patients with CFS and 60 nonfatigued, healthy controls (NF) enrolled in a population-based case-control study in Wichita (KS, USA). We used traditional biostatistical methods to measure the association of high AL to standardized measures of physical and mental functioning, disability, fatigue and general symptom severity. We also used nonlinear regression technology embedded in machine learning algorithms to learn equations predicting various CFS symptoms based on the individual components of the allostatic load index (ALI).

Methods: An ALI was computed for all study participants using available laboratory and clinical data on metabolic, cardiovascular and hypothalamic-pituitary-adrenal (HPA) axis factors. Physical and mental functioning/impairment was measured using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36); current fatigue was measured using the 20-item multidimensional fatigue inventory (MFI); frequency and intensity of symptoms was measured using the 19-item symptom inventory (SI). Genetic programming, a nonlinear regression technique, was used to learn an ensemble of different predictive equations rather than a single one. Statistical analysis was based on the calculation of the percentage of equations in the ensemble that utilized each input variable, producing a measure of the 'utility' of the variable for the predictive problem at hand. Traditional biostatistics methods include the median and Wilcoxon tests for comparing the median levels of subscale scores obtained on the SF-36, the MFI and the SI summary score.

Results: Among CFS patients, but not controls, a high level of AL was significantly associated with lower median values (indicating worse health) of bodily pain, physical functioning and general symptom frequency/intensity. Using genetic programming, the ALI was determined to be a better predictor of these three health measures than any subcombination of ALI components among cases, but not controls.

Allostatic load (AL) has been described as a measure of the cumulative wear and tear on the body resulting from chronic or inadequate adaptation to change [1]. According to this paradigm, adaptation to change in the everyday environment, as well as adaptation to non-routine challenge, such as acute/chronic disease and physical/emotional trauma, represent sources of stress [1]. Response to stress is orchestrated by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) via the production of stress hormones including cortisol, epinephrine, dihydroepiandrosterone sulfate (DHEA-S) and noradrenalin [2]. High baseline levels of AL have been associated with cardiovascular disease (CVD), mortality and decline in physical and cognitive functioning in a prospective study of 70–79 year old persons over a 7-year period [3,4]. In addition, specific components of AL were differentially associated with cognitive decline and

CVD [3,4], although the overall AL index (ALI) was found to be the best predictor of physical decline [4].

A companion paper in this issue describes an association between chronic fatigue syndrome (CFS) and AL (see Maloney and colleagues [5]). Patients with CFS were almost two times more likely to have a high allostatic load compared with healthy nonfatigued controls. Recently, an empiric definition of CFS has been described based on an algorithm that uses scores from three data collection instruments that measure fatigue, disability, and symptom frequency and severity [6]. These instruments provide for quantitative assessment of eight parameters of physical and mental functioning and subsequent impairment, five parameters of fatigue, and overall symptom severity for eight CFS-defining symptoms. Among the groups of CFS cases and controls, we analyzed the association of AL level with levels of physical and mental health,

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impairment, fatigue and symptom severity using standard biostatistical approaches. In addition, we used genetic algorithms to analyze whether the ALI, or its components, best predicted the health parameters found to be associated with AL in conventional biostatistical analyses.

Methods

Study subjects

We conducted a population-based case-control study of CFS in Wichita (KS, USA) and identified 43 CFS cases and 60 nonfatigued, healthy controls (NF) (see Vernon and Reeves in this issue for details on study design and disease classification [7]). Briefly, patients with CFS were matched on a 1:1 basis with nonfatigued controls based on age, sex, race, and body mass index (BMI). Following reclassification of cases according to an empiric criteria [6], and exclusion of cases with major depressive disorder with melancholic features (MDDM), precise matching of cases to controls was not maintained. However, the remaining cases and controls were highly similar with respect to distributions of age, sex, race and BMI (Table 1).

Data collection

Data on demographic variables was collected by a self-administered questionnaire.

During a 2-day hospital stay, a research nurse obtained measures of blood pressure, weight, height, and waist and hip circumference. Blood pressure was measured after half an hour of rest. Waist circumference was measured at the narrowest point between the ribs and the iliac crest; hip circumference was measured at the maximal buttocks. BMI was computed based on the ratio of weight in kilograms to height in meters squared (kg/m^2).

Cases and controls completed self-administered questionnaires and used standardized instruments at home that measured their current level of mental and physical functioning and impairment (Medical Outcomes Study 36-item Short Form Health Survey [SF-36]), current fatigue (20-item multidimensional fatigue inventory [MFI]) and frequency and intensity of symptoms (19-item symptom inventory [SI]). A research nurse reviewed all data collection instruments for completeness of information during the clinic visit. For the purposes of this analysis, all subscales of the MFI, as well as the SI instruments, were rescaled to range from 0–100 to be consistent with the scaling of the SF-36. As such, 0 represented the worst score and 100 represented the best score with respect to health, functioning and symptoms.

Laboratory methods

During a 2-day hospital stay, a research nurse conducted venipunctures to draw blood for sera, plasma and cells. A 24-hour urine specimen was collected by each study subject during clinic. Albumin was measured in heparinized plasma. C-reactive protein (CRP), aldosterone and dihydroepiandrosterone sulfate (DHEA-S) were measured in serum. Interleukin-6 (IL-6), epinephrine and norepinephrine were measured in plasma. Cortisol was measured from a 24-hour urine sample. For details on specimen collection, processing and laboratory testing, please see a companion paper in this issue [7].

Allostatic load index

We measured AL using 11 components representing metabolic and cardiovascular activity, inflammatory response, HPA-axis activity and SNS activity. Metabolic activity was measured by the waist:hip ratio. Cardiovascular activity was measured by diastolic and systolic blood pressure and aldosterone; inflammation markers included serum measurements of CRP and albumin, which is inversely related to CRP, and plasma level of IL-6, a proinflammatory cytokine; HPA-axis function was measured by 24-hour measure of urinary cortisol and serum DHEA-S, a cortisol antagonist. SNS activity was measured by plasma levels of epinephrine and norepinephrine. Sex-specific cut-offs were determined for waist:hip ratio, cortisol and DHEA-S due to sex differences in these measurements. Risk cut-offs for these 11 factors were based on quartile risk levels (i.e., 25th percentile or 75th percentile) determined for the nonfatigued controls in this study, except for blood pressure indices, which were based on clinical reference values. An ALI was determined for each study subject based on the total number of components in which the subject's measurement scored in the high-risk category. Dichotomous levels (high–low) of AL were determined based on the median level of AL among controls (median = 2). A categorical measure of AL included three categories with values of low (< 2), medium (3–4) and high (5–7).

Statistical methods

The nonparametric median tests were used to compare median levels of allostatic load between cases and controls, using PROC NPAR1WAY in SAS Version 9.0 (SAS Institute, NC, USA). The median and Wilcoxon tests were also used to examine associations between symptoms of illness and allostatic load within case and control

study groups. Specifically, we compared median scores on eight scales that measured physical functioning and impairment (SF-36 instrument), five scales that measured fatigue (MFI instrument) and the summary score for the eight CFS-defining symptoms (SI instrument) between high and low categories of the allostatic load in separate analyses conducted among CFS cases and controls.

We then applied a genetic programming (GP)-based symbolic regression algorithm to interrogate relationships between the components of ALI and the symptoms that were found to be significant in the analysis described above. As this well-known computer science algorithm is not yet common in the biomedical community, we will first make a few comments regarding its appropriateness in the present context, and then present the details of our application of the technique.

In problems where one wishes to understand the nature of the dependency of one variable upon a number of others, as displayed in some datasets, the standard solution is to make appropriate assumptions about how the dependent variable might be conditioned on, or related to, the independent variables, and then carry out a regression analysis using, for example, ordinary least squares or discrete dependent variable methods. However, these standard approaches present well-known shortcomings. The data may display nonlinear dependencies that these mathematical techniques are not capable of capturing. Extending the scope of these techniques is possible, but involves making particular data transformations and assumptions that have the result of inserting the researcher's bias very strongly into the data analysis process.

In contrast to standard regression analysis, GP-based symbolic regression, as originally introduced in [8], involves the use of a computer simulation of the evolutionary process to 'evolve' simple computer programs or mathematical functions that are a good fit to a given set of data. These programs are built up from primitives specified by the researcher, which may include, for example, logical and arithmetic operators, or more complex control structures. In the present work we have used only arithmetic operators (+, -, *, /), which means that we are using GP-based symbolic regression effectively as a nonlinear regression algorithm where the class of nonlinear functions involved is restricted to the rational functions.

Overall, symbolic regression is a relatively difficult and computation-intensive process. How-

ever, recent algorithmic advances coupled with faster computers have enabled the application of symbolic regression to a wide variety of data sets. Among the general benefits of symbolic regression include human insight and interpretability of model results, identification of key variables and variable combinations, and the generation of computationally simple models.

The key parameters of the GP process are the population size and the number of generations. The evolutionary learning process begins with an initial population of random guesses, then rates each guess as to the quality of its fit to the data (its 'fitness'), then generates new guesses by applying mathematical 'crossover' and 'mutation' operators to the fitter among the already-evaluated guesses. This process is then iterated until the initially specified number of generations has passed, with the result that the population of guesses gradually improves as the simulated evolution proceeds.

The insight obtained from GP symbolic regression may be maximized by looking beyond the individual functions learned and studying the overall ensemble of functions produced by the evolutionary process. Such ensembles may be built up by running GP multiple times on the same dataset, since GP is a stochastic process and may give slightly different answers each time. For instance, some fit regression functions may ignore certain variables; and others may ignore other variables. Given an ensemble of functions learned by the GP based on the same data, one may study which variables and variable combinations tend to occur most often in the functions in the ensemble – a powerful way of understanding which of the independent variables are most important in determining the dependent variable, not merely on their own, but in terms of their nonlinear combinations with other independent variables.

Our genetic algorithm used a population size of 150 and 100 generations, with a mutation rate of 0.01 and an operator set consisting of the four standard arithmetic operators plus floating-point constants. GP with these parameters was run 100 times to generate a large model ensemble. The fitness of a candidate equation evolved by GP was defined as the average error of its predictions. We ran the evolutionary process 100 times in order to generate a diverse ensemble of regression functions. For each of the symptom quantities being predicted, we calculated the error statistics (mean and standard deviation) of the best results from all the 100 GP runs. We

Table 1. Distribution of matching factors among patients with chronic fatigue syndrome and nonfatigued controls.

Factors	CFS case (n = 43)	NF controls (n = 60)
Age		
Mean (SD)	50.6 (8.7)	50.5 (8.6)
Range	(27.0–69.0)	(31.0–69.0)
Sex (n [%])		
Female	36 (83.7)	48 (80.0)
Male	7	12
Race (n [%])		
Caucasian	40 (93.0)	56 (93.3)
Black/other	3	4
Body mass index		
Mean (SD)	29.4 (4.4)	28.6 (4.9)
Range	(23.0–40.0)	(16.0–40.0)

CFS: Chronic fatigue syndrome; NF: Non fatigued; SD: Standard deviation.

also calculated the utility value of each independent variable (each variable used as input to the regression functions), defined as the percentage of high-quality regression functions that contain the given variable. If variables have markedly different utilities for predicting the same dependent variable across different patient sets, for example, CFS versus NF, then this suggests a possible biological difference between the patient sets. The GP regression implementation used was that contained in the Biomind ArrayGenius software package (Biomind LLC, MD, USA).

Results

Our analysis is based on data collected among 43 CFS patients and 60 NF controls. CFS patients and controls were on average, 50 years old, predominantly female and Caucasian, with an average BMI of approximately 29 (Table 1). Given that CFS patients were almost two times more likely to have a high level of AL compared with NF controls (see the companion paper by Maloney and colleagues in this issue [5]), we examined whether a high level of AL was associated with poor mental and physical health, impairment, fatigue and symptom frequency/severity among CFS patients. Median values for all subscales by AL category within groups of CFS patients and NF controls are shown in Table 2. The SF-36 instrument measures eight parameters of mental and physical functioning. We compared the median scores for the eight scales of the SF-36 between cases who had high levels of AL and cases who had low levels of AL. CFS cases with a high level of AL had

a significantly lower median score (worse outcome) on the subscale measuring bodily pain than CFS cases with a low level of AL ($p = 0.009$) (Figure 1). Among CFS cases, median bodily pain score decreased across levels of low, medium and high AL in a significant linear trend ($p = 0.02$) (Figure 2).

CFS cases with a high level of AL had a significantly lower median score on the subscale measuring physical functioning than cases with a low AL ($p = 0.02$) (Figure 1). None of the other measures of physical or mental functioning on the SF-36 were associated with AL among cases.

We next examined whether AL was associated with frequency and severity of the eight case-defining CFS symptoms [9] among CFS patients, as measured by a summary score on the SI instrument. CFS patients with high levels of AL had a significantly lower median symptom summary score (worse outcome) compared with CFS patients with low levels of AL ($p = 0.049$) (Figure 3). However, the symptom summary score did not decrease in a linear trend with increasing levels of AL ($P_{\text{trend}} = 0.14$). Finally, we examined whether a high AL was associated with lower median scores (worse outcome) for fatigue as measured by the five scales of the MFI among CFS patients. The median scores on all scales of the MFI were similar between CFS patients with high and low levels of AL (Table 2). Among controls there were no statistically significant associations between AL level and physical or mental functioning, or impairment, symptom frequency/severity and fatigue as measured by scores on subscales of the SF-36, MFI and SI summary score (Table 2).

Table 2. Median scores for SF-36 and MFI subscales, and symptom inventory summary score, by allostatic load category for chronic fatigue syndrome patients and nonfatigued controls.

Instrument subscale	CFS cases		NF controls	
	Low AL (n = 18)	High AL (n = 25)	Low AL (n = 33)	High AL (n = 27)
SF-36 bodily pain	51.0	41.0	84.0	84.0
SF-36 physical functioning	67.5	50.0	95.0	90.0
SF-36 mental health	68.0	68.0	92.0	88.0
SF-36 role emotional	66.7	33.3	100.0	100.0
SF-36 role physical	12.5	0.0	100.0	100.0
SF-36 social functioning	50.0	50.0	100.0	100.0
SF-36 vitality	20.0	15.0	75.0	80.0
SF-36 general health	52.0	52.0	87.0	90.0
MFI – reduced activity	35.0	35.0	75.0	75.0
MFI – general fatigue	10.0	10.0	60.0	65.0
MFI – mental fatigue	25.0	25.0	65.0	75.0
MFI – reduced motivation	37.5	45.0	70.0	75.0
MFI – physical fatigue	25.0	30.0	65.0	70.0
Symptom inventory score	77.0	68.0	98.0	99.0

AL: Allostatic load; CFS: Chronic fatigue syndrome; MFI: Multidimensional fatigue inventory; NF: Nonfatigued; SF-36: 36-item Short Form Health Survey.

We next applied GP-based nonlinear regression to further examine the relationship between AL and the three measures of bodily pain, physical functioning and the symptom summary score. We used this technique to discover functional relationships between these three scores and the components of the ALI to try to discover which components of ALI were driving these symptoms. For each score we used GP to learn two ensembles of predictive relationships, one consisting of relationships based on AL and the other consisting of relationships based on combinations of AL components. We found that within the CFS, but not the control group, AL may be effectively used as a predictor of these three scores. Among the CFS group, the GP search algorithm did not find nonlinear combinations of the AL components that had significantly greater predictive power than the ALI (Table 3). This observation is based on the smaller predictive errors for these three parameters in the ensemble of models based on the ALI compared with the models based on other formulations using the components of ALI.

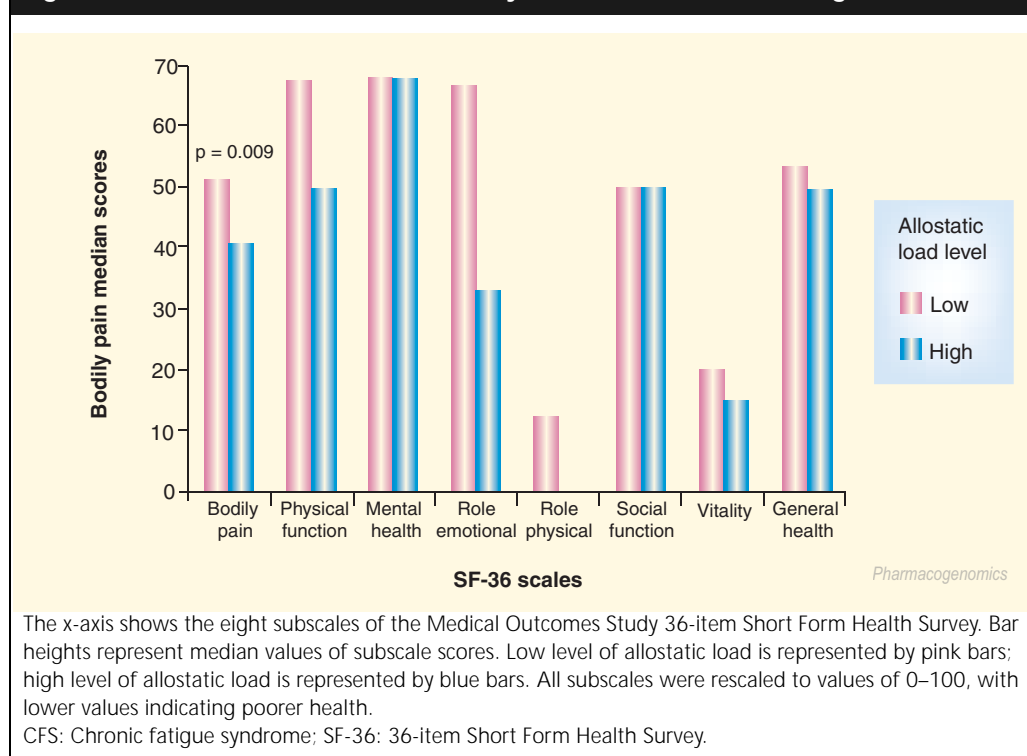
Among CFS cases, we further measured the utility of individual AL components in predicting the three scores for bodily pain, physical functioning and overall symptom frequency/severity. The utility of a component for predicting a score was

defined as the percentage of successful predictive relationships (defined as relationships appearing in the final generation of one of the series of GP runs for that score) including that component. Bodily pain was best predicted by the CRP AL factor, which had a utility value of 0.9 (Table 4). Physical functioning was best predicted by the norepinephrine risk factor, epinephrine risk factor and diastolic blood pressure AL factor, which had utility values ranging between 0.78–0.75 (Table 4). Physical function does rely on changes in norepinephrine and epinephrine levels and subsequent changes in diastolic blood pressure for maintenance of blood flow to the brain and to the rest of the body. The overall symptom summary score was best predicted by the systolic blood pressure risk factor, followed by the aldosterone AL factor (utility values of 0.83 and 0.72, respectively) (Table 4). If there were primary or secondary problems in these latter two parameters, physical functioning would be adversely affected [10].

Discussion

We examined the association between the ALI and quantitative scores measuring physical and mental health and impairment, fatigue and symptom frequency/severity, and found that a high ALI was associated with worse median scores for bodily pain, physical functioning and overall symptom

Figure 1. Median values of SF-36 scales by allostatic load level among CFS cases.

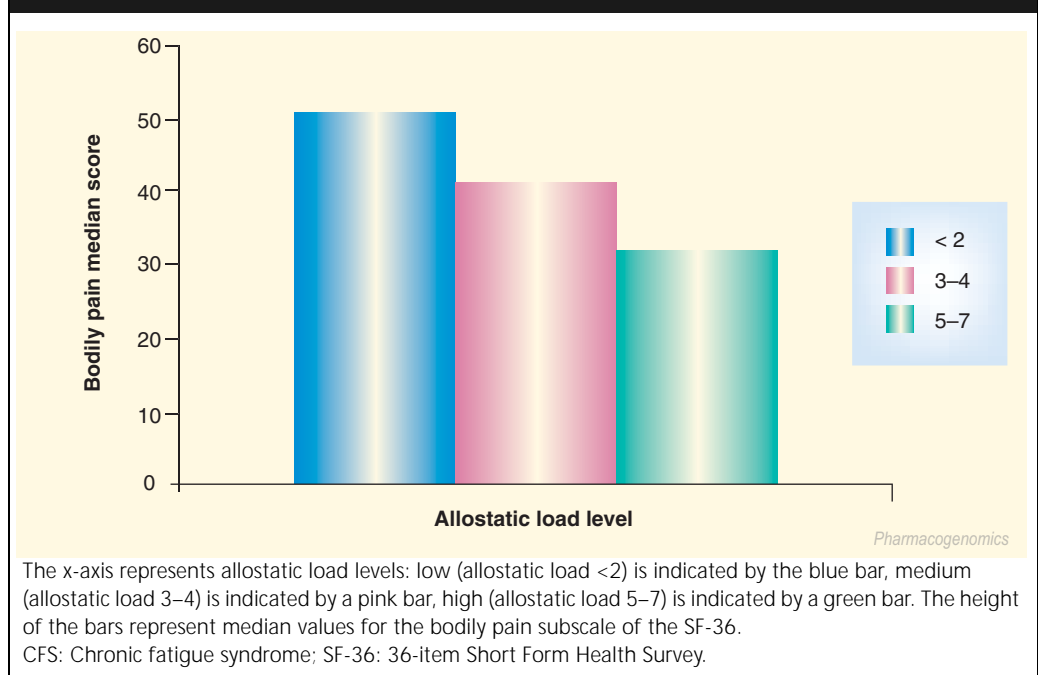


frequency/severity, among CFS patients, but not NF controls. Since bodily pain and physical functioning essentially represent the physical health component of the SF-36, and the symptom summary score represents CFS-specific symptoms, these results support the association between AL and CFS, which is suggested in a companion paper by Maloney and colleagues in this issue [5], and suggest that AL is related to physical decline, rather than mental decline in CFS patients. Among CFS cases, the ALI appeared to be a better predictor of these three factors than any other nonlinear combination of its components when analyzed using 100 generations of a genetic algorithm. In other words, all components of AL seem to be important, and the way the AL formula combines them seems reasonable, since a powerful nonlinear regression algorithm failed to find a better combination. These results are consistent with Seeman and colleagues, who reported that none of the individual factors or subgroups of factors comprising AL were as good as the summary ALI for predicting decline in physical functioning [4].

To further investigate the importance of the different AL components in predicting scores for bodily pain, physical functioning and symptom summary score, we used genetic programming to compute utility values for AL components in separate analyses for each of the three health

parameters. We found that different components were the best determinants of the three parameters. Specifically, the CRP AL factor was the best predictor of bodily pain. The bodily pain subscale of the SF-36 is a measure of pain magnitude and the degree that pain interferes with functioning [11]. We are not aware of any other reports of an association between AL and bodily pain determined by the SF-36, whereas reports of pain in musculoskeletal disorders in general are associated with low scores on the SF-36 [12].

Physical functioning, as measured by the SF-36, is a measure of physical activity ranging from activities of daily living (ADL) to vigorous activity [11]. We found that three AL factors best predicted physical functioning, including norepinephrine, epinephrine and diastolic blood pressure. Our results are similar to those reported for a prospective study of healthy, elderly men and women who participated in the Successful Aging Study. Karlamangla and colleagues determined that decline in physical (and cognitive) functioning over a 7-year period were best predicted by hormonal/endocrine factors including epinephrine and cortisol, independent of metabolic factors [3]. In addition, Karlamangla and colleagues also found diastolic blood pressure to be the best predictor of cognitive, but not physical decline [3].

Figure 2. Median values for bodily pain by allostatic load level among CFS cases.

The summary symptom score is a measure of the frequency and intensity of the eight CFS-defining symptoms measured in the symptom inventory [6]. Those eight symptoms include unusual postexertional fatigue, impaired memory or concentration, unrefreshing sleep, headaches, muscle pain, joint pain, sore throat, and tender cervical lymph nodes. We found that systolic blood pressure and aldosterone AL factors best predicted the summary symptom score among CFS cases. These factors both represent the cardiovascular component of the ALI. Patients with CFS were excluded from this study if they had ever suffered a myocardial infarction or stroke, so this relationship is not likely to suggest that overt cardiovascular disease is underlying the relationship between the cardiovascular component of AL and the summary symptom score. Perhaps more subtle cardiovascular abnormalities account for this relationship. A high level of angiotensin-converting enzyme (ACE) activity was detected in CFS patients compared with controls with sarcoidosis [13]. In addition, a companion paper in this issue (Gurbaxani and colleagues [14]) reported that the R-R interval, as measured by electrocardiogram, was the most important factor to discriminate CFS patients from controls. Perhaps our data are also suggesting an association between cardiovascular abnormalities and CFS symptoms.

It is interesting that fatigue as measured by the MFI, which is the perceived hallmark of the syndrome and is required for diagnosis, was not

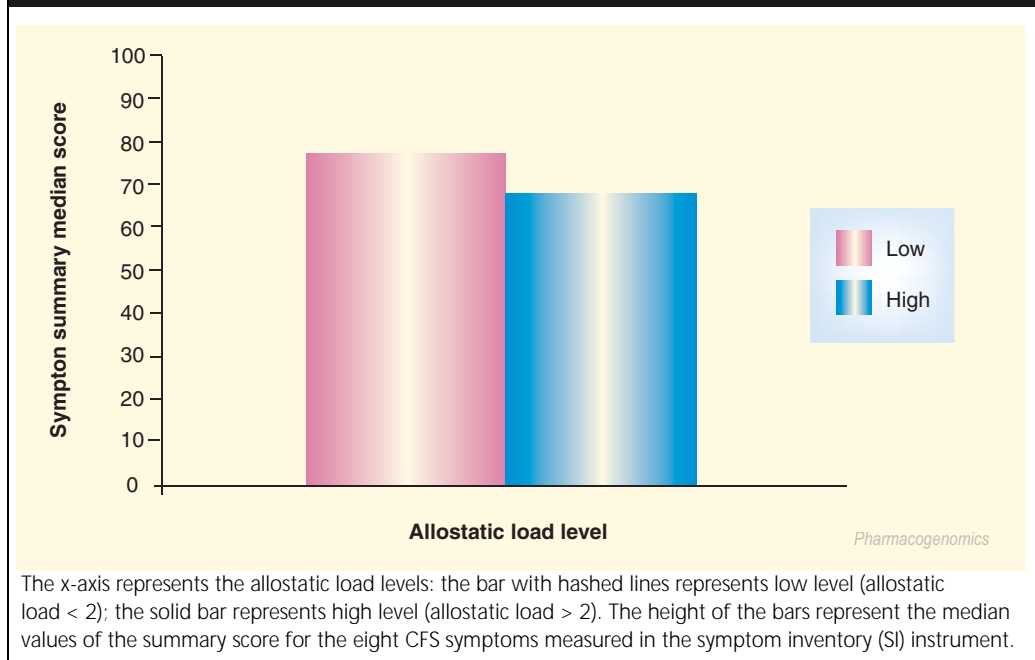
associated with the magnitude of the AL among CFS cases. However, we know of no reports citing an association between AL and fatigue in the literature.

Among controls, we did not find any significant associations between AL and scores for mental or physical health or impairment, fatigue or symptom summary score. This result was supported by genetic programming analysis that found the ALI to be a poorer predictor of bodily pain, physical functioning and symptom summary scores compared with other nonlinear combinations of the ALI components. It is known that CFS cases consistently score worse on all subscales of the SF-36, MFI and SI summary score compared with controls. It seems reasonable that ALI would only have a good predictive capability when some threshold level of mental and/or physical impairment is present. Hellhammer and colleagues also found no association between AL and subjective complaints in a study of 25-40 year olds, and over 60 year olds [15].

Outlook

Individual responses to daily life and to stressful events, including infectious and other diseases, trauma and psychiatric challenges, create a changing, but cumulative biological and psychiatric record that can be estimated as AL. Establishment of methods to quantify the importance of the overall load and its component factors will be helpful in predicting the development of disease.

Figure 3. Median values of symptom inventory (SI) by allostatic load level among CFS cases.



If, for example, factors associated with specific diseases can be identified prior to expression of the disease, preventive intervention can be initiated.

Since the brain processes and stores input from within and from outside the body and responds to this assembled information at conscious (adaptive/maladaptive) and/or unconscious (physiological and biochemical) levels, an additional benefit from the types of evalua-

tions performed in this study would be identification of the origin of output signals construed as AL. Do the measured components of AL represent afferent or efferent processes? If the responses are purely those of the brain responding to altered levels of blood volume or other viscerotropic signals, control could be effected at the physiological/biochemical (pharmacologic) levels. If the

Table 3. Average predictive error and standard error of the best predictive models for bodily pain, physical functioning and symptom summary score in CFS cases and controls.

Subset	Inputs used	Symptom predicted	Best result	
			Average	SD
CFS	Allostatic load index	Bodily pain	10.9	8.2
		Physical function	17.5	10.2
		Symptom summary	12.1	10.7
	Allostatic load components	Bodily pain	11.4	9.8
		Physical function	19.8	11.4
		Symptom summary	12.4	10.0
Control	Allostatic load index	Bodily pain	11.9	10.7
		Physical function	9.0	9.2
		Symptom summary	3.6	3.6
	Allostatic load components	Bodily pain	11.0	10.7
		Physical function	7.7	9.4
		Symptom summary	3.2	4.2

CFS: Chronic fatigue syndrome; SD: Standard deviation.

Table 4. Utility of allostatic load components for predicting bodily pain, physical function and symptom summary in CFS patients.

Allostatic load component	Utility
<i>Bodily pain</i>	
CRP_RISK	0.9
DIS_BP	0.64
ALBUMIN_RISK	0.59
DHEA_RISK	0.53
EPINEPH_RISK	0.52
CORT_RISK	0.49
IL6_RISK	0.49
NOREPINEPH_RISK	0.48
ALDOST_RISK	0.47
SYS_BP	0.46
<i>Physical function</i>	
NOREPINEPH_RISK	0.78
DIS_BP	0.75
EPINEPH_RISK	0.75
CRP_RISK	0.67
ALBUMIN_RISK	0.66
SYS_BP	0.63
DHEA_RISK	0.6
CORT_RISK	0.58
IL6_RISK	0.57
ALDOST_RISK	0.45
<i>Symptom summary</i>	
SYS_BP	0.83
ALDOST_RISK	0.72
DHEA_RISK	0.66
DIS_BP	0.66
NOREPINEPH_RISK	0.62
CRP_RISK	0.59
CORT_RISK	0.54
ALBUMIN_RISK	0.5
IL6_RISK	0.36
EPINEPH_RISK	0.36

ALDOST: Aldosterone; CFS: Chronic fatigue syndrome; CORT: Cortisol; CRP: C-reactive protein; DHEA: Dehydroepiandrosterone; DIS_BP: Diastolic blood pressure; EPINEPH: Epinephrine; IL6: Interleukin-6; NOREPINEPH: Norepinephrine; SYS_BP: Systolic blood pressure.

responses are driven, at least in part, by the individual's interpretation of them at a conscious level and nonconstructive behaviors contribute to the measured components, learning about the linkages and altering behavior could affect positive adaptive responses.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency.

Highlights

- Among chronic fatigue syndrome (CFS) patients, a high allostatic load (AL) was progressively associated with worse bodily pain and also associated with worse physical functioning and worse symptom frequency/intensity.
- In each case, the genetic programming (GP) search algorithm did not find nonlinear combinations of the AL components with significantly greater predictive power than the allostatic load index (ALI) itself for predicting bodily pain, physical functioning and symptom summary score.
- The utilities of the different AL components were quite different in predicting the scores for bodily pain, physical functioning and symptom summary among CFS cases
- AL was not associated with the scores obtained for the three health parameters of interest among controls. Similarly, the GP search algorithm did not find the ALI to have the best predictive power compared with other combinations of AL factors.
- AL is not a predictor of fatigue *per se*.

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