Published in final edited form as:

J Hum Behav Soc Environ. 2012 October 1; 22(7): 822–833. doi:10.1080/10911359.2012.707896.

Predictors of Fatigue among Patients with Chronic Fatigue Syndrome

Leonard A. Jason, Molly Brown, Meredyth Evans, and Abigail Brown
DePaul University

Leonard A. Jason: ljason@depaul.edu; Molly Brown: molly.brown@yale.edu; Meredyth Evans: meredyth.evans@gmail.com; Abigail Brown: abrown57@depaul.edu

Abstract

Activity logs involve patients writing down their activities over one or more days. Several studies have found these data collection instruments to accurately describe activities of patients with chronic fatigue syndrome (CFS). The purpose of this study was to utilize the repeated measures available on the ACTRE to evaluate predictors of fatigue at a given timepoint. A random intercept model was tested with the following variables predicting current fatigue: past fatigue (30 mins. prior), current category of activity (e.g., resting, work, recreation, etc.), past category of activity (30 mins. prior), the interaction of past fatigue and past activity, and TH2/TH1 immune shift. These findings and others suggest that activity logs can provide investigators and clinicians with valuable sources of data for understanding patterns of behavior and activity among patients with CFS.

Chronic fatigue syndrome (CFS) is an illness marked by decreased vitality and increased symptom severity after exertion. As a result, many patients with CFS report that avoidance of overexertion through activity pacing is a preferred method of illness management (Cooper, 2001). The envelope theory (Jason, Melrose, et al., 1999) was proposed as a model of pacing activities among patients with this illness. This theory suggests that by maintaining expended energy levels within the “envelope” of perceived available energy levels, patients can maintain an optimal level of functioning based on individual capabilities. Dramatic increases in fatigue, or “crashes,” can be prevented through maintaining activity levels within the energy envelope (Jason, Melrose, et al., 1999). Patients with CFS can rate their weekly level of available and expended energy with good inter-rater reliability (Hawk, Jason, & Torres-Harding, 2007). In support of this envelope theory, using time series analyses, energy expended, physical exertion, and mental exertion were positively related to actigraphy (the electronic measurement of activity levels) (Jason, Tryon, Frankenberry, & King, 1997). In addition, a positive significant relationship between current fatigue level and the amount of energy that participants perceived they had used two-days prior has been found (Jason, Tryon et al., 1999).

Remaining within one’s envelope requires monitoring of activity and fatigue throughout the day. Some research has demonstrated that fatigue levels among patients with CFS are highest in the morning and evening hours (Stone et al., 1994; Wood, Magnello, & Sharpe, 1992), suggesting that patients may be particularly vulnerable to overexertion during these times. However, these fatigue patterns were not evaluated in conjunction with activity level. Several methods of assessment have been employed to evaluate fatigue and/or activity patterns among patients with CFS, including actigraphy, an objective measure of activity

(Tryon, Jason, Frankenberry, & Torres-Harding, 2004; van der Werf, Prins, Vercoulen, van der Meer, & Bleijenberg, 2000); electronic diaries (Stone et al., 1994); and paper-and-pencil activity records (Jason et al., 2009).

Self-report assessments, such as the National Institutes of Health Activity Record (ACTRE; Gerber & Furst, 1992), allow individuals to rate feelings of fatigue, pain, type and intensity of activities, and enjoyment and meaningfulness of activities every 30 minutes. The ACTRE has utility for clinicians, as they can obtain a composite that represents a comprehensive profile of functioning as well as areas of dysfunction (Gerber & Furst, 1992). Using this instrument, Hawk, Jason, and Pena (2007) found participants with CFS spent significantly more time resting than those with Major Depressive Disorder or a control group. The CFS group spent nearly 2.5 times longer resting than the Major Depressive Disorder group and 4 times longer than the control group when performing a low intensity activity. This study found that those with CFS feel fatigued more of the time, find activity to be fatiguing more of the time, and need more rest during activity than people with Major Depressive Disorder.

In another sample of patients with CFS, Jason et al. (2009) found that the percent of time spent feeling fatigued was positively associated with a higher percent of time in pain and doing activities that were fatiguing. However, time spent in meaningful activities was associated with less fatigue. It is very possible that the use of these types of activity logs could help investigators better understand the relationship between types of activity engagement and functioning. In another study using the ACTRE, Jason and Brown (2011) examined fatigue intensity, variability and slope. Three clusters emerged involving patients with different trajectories over a one day period of time. One group had high fatigue intensity, low variability and fatigue intensity, and stayed the same over time. A second group had moderate fatigue intensity, high variability, and a decrease in fatigue intensity over time. A third group had moderate fatigue intensity and high variability, but with an increase in fatigue intensity over time. These three clusters of patients did differ on measures of actigraphy, pain, and immune functioning.

Several researchers have found a shift from TH1 to TH2 cytokines among patients with CFS (Antoni et al., 2003; Skowera et al., 2004). In the TH1 response, the T-helper cell produces pro-inflammatory cytokines, which activate T-cytotoxic cells as well as natural killer cells (Segerstrom & Miller, 2004), and contribute to the clearance of intracellular pathogens. In contrast, the TH2 pathway involves major anti-inflammatory cytokines, which promote humoral immunity by differentiation of B cells into antibody-secreting B cells and B cell immunoglobulin switching to IgE. These anti-inflammatory cytokines inhibit production of pro-inflammatory cytokine and T-cell proliferation. Whereas a highly anti-inflammatory response minimizes inflammation, it can allow existing intracellular infections to linger. Little is known about the relationship between TH2/TH1 cytokines and momentary fatigue levels.

The ACTRE and other momentary behavioral assessments are often reported as composite scores (Friedberg & Sohl, 2009), as opposed to moment-to-moment relationships among activity and fatigue variables. The purpose of this study was to utilize the repeated measures available on the ACTRE to evaluate self-report and biological predictors of fatigue at a given timepoint. Based on the envelope theory (Jason et al., 1999), it is hypothesized that fatigue intensity and type of activity will predict fatigue intensity at the subsequent half hour. Fatigue and activity interaction effects, and TH2/TH1 shift predicting current fatigue were also explored.

Method

Participant Recruitment

Participants were recruited for a non-pharmacologic treatment trial for CFS (Jason et al., 2007) from a variety of sources including physician referrals, advertisements in local newspapers, and announcements at local CFS support group meetings. Participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Participants met the Fukuda et al. (1994) criteria for CFS. Medical and psychiatric examinations were performed to rule out exclusionary conditions according to the Fukuda et al. criteria. A total of 114 participants were recruited for the original study. Twenty four participants did not complete the ACTRE, therefore 90 participants were included in the present investigation.

Materials

Activity Record—The ACTRE is a daily self-administered log of physical activity and symptoms (Gerber & Furst, 1992). Respondents log their activities, fatigue, and pain every half-hour over the course of two days. In a validation study of the ACTRE, Gerber and Furst (1992) demonstrated that the ACTRE had adequate psychometric properties as a measure of activity and functional status in a population with a chronic disabling condition. The ACTRE is significantly correlated with other measures of fatigue (Gerber & Furst, 1992).

For this study, ACTRE data for one day were used to evaluate predictors of momentary fatigue. On the ACTRE, fatigue is rated on a four-point scale in response to the question, “At the beginning of this half-hour I felt fatigue,” with 1 = not at all; 2 = very little; 3 = some; and 4 = a lot. Of particular interest in this study was the association of activity and fatigue. Thus, the second ACTRE item used was type of activity, which was rated by participants in nine categories: rest; self-care; preparation or planning; household activities; work; recreation or leisure; transportation; treatment; and sleep. Fatigue and activity ratings were only counted when participants were awake, as fatigue ratings are likely invalid when asleep.

Flow Cytometry—One hundred microliters of heparinized whole blood was incubated for 15 minutes at room temperature with optimal concentrations of fluorochrome conjugated antibodies CD45 (Fluorescein [FITC]), CD14 (Phycoerythrin RD1), CD3-(Phycoerythrin CY5 [PC5]), CD8 (Phycoerythrin-Texas Red [ECD]), CD45RA (FITC), CD62L (Phycoerythrin, PE), CD2 (FITC), CD26 (PE), CD4 (ECD) CD8 (PC5) and isotype controls, in 4 color combinations for 15 min, 25°C. Samples were then fixed and lysed with Optilyse-C reagent, followed by analysis on an XL-MCL flow cytometer. All reagents and instrumentation were from Beckman Coulter Corporation, Hialeah, Florida. Analyses were performed by collecting 2500 events in the lymphocyte region. All determinations were corrected for purity by dividing by the percent CD45+CD14– events in the lymphocyte gate. Absolute count for each of the subsets was calculated by multiplying the percent positive for each marker by the lymphocyte count determined from the automated complete blood count (CBC). CBC was performed on a Coulter MAX-M (Coulter Corporation, Hialeah, FL). Accuracy and precision of analyses were optimized through the adherence to the CDC’s recommendations for flow cytometric analyses (Centers for Disease Control and Prevention, 1997). Lymphocyte, monocyte and granulocyte populations were determined using light scatter and back gating on fluorescence for the CD45 bright and CD14 negative population. The isotype controls were the reference for negative events. Spectral compensation was established daily. Quality control included the optimization for lymphocyte recovery, purity of the gate of analysis, lymphosum.

In a non-pharmacologic intervention study, Jason, Torres-Harding, et al. (2008) found those who had a decreased T and B cells and an elevated percentage of natural killer cells were most likely to improve after treatment, while those who had higher Total B cell (CD19+) scores were less likely to improve. In other words, improvers had a more cellular Type 1 immune response as indicated by the relatively expanded cytotoxic subsets (CD8, CD56). Non-improvers had an elevated humoral immune response (B Cell), or a dominance of the Type 2 over the Type 1 immune response. Data for this study included Total CD8 % which is the total number of CD8 positive cells, with lower counts indicating lower anti-viral immune responses (lower TH1). Jason, Torres-Harding and colleagues (2008) also inspected the total number of CD56 cells (including CD3+ and CD3-), with higher scores suggesting a more cellular type (TH2) response. TH2/TH1 was calculated as a ratio, with higher numbers meaning more of a TH2 shift.

Statistical Analysis

A multilevel analysis was conducted in SAS 9.2. Specifically, at the person level (i.e., level-1), categorical values of activity were dummy coded with resting indicated as the baseline category and used to predict present level of fatigue. Additionally, the types of activities individuals were engaged in during a specific time period (i.e., a half hour prior) were dummy coded and used as predictors (i.e., lagged activity), with resting serving as the baseline category. Finally, past level of fatigue was used to predict present fatigue. Individuals were allowed to vary from person to person in terms of their average level (i.e., a random intercept). Finally, the TH2/TH1 ratio was a person-level variable entered as a level-2 predictor. For heuristic purposes and ease of representation, rather than writing all parameters, the eight activities are represented in one variable; the true model would have seven slopes, with one per activity. Overall, the following model was estimated, where categorical variables represent eight separate activities represented by seven dummy vectors and their corresponding slopes:

$$\begin{aligned}
 \text{Present Fatigue}_{ij} = & b_0 + b_1 \text{Present Activity}_{i,j} \\
 & + b_2 \text{Past Fatigue}_{i,j-1} \\
 & + b_3 \text{Past Activity}_{i,j-1} \\
 & + b_4 \text{Past Fatigue} \\
 & \times \text{Past Activity}_{i,j-1} + e_{ij}
 \end{aligned}
 \quad \text{Level 1}$$

$$\begin{aligned}
 b_0 = & \beta_0 + \beta_5 \text{TH2TH1}_i + v_{0i} \\
 b_1 = & \beta_1 \\
 b_2 = & \beta_2 \\
 b_3 = & \beta_3 \\
 b_4 = & \beta_4
 \end{aligned}
 \quad \text{Level 2}$$

Results

Demographics

Of the 90 participants, 84.4% were women. In terms of ethnicity, 87.8% were Caucasian, 5.6% were African American, 3.3% were Latino, and 3.3% were Asian American. For employment status, 55.6% were unemployed and 44.4% were employed. The mean age of participants was 44.16 years (standard deviation = 10.72). Participants on average had been diagnosed with CFS for 8.61 years (standard deviation = 6.16).

Overall Summary

Those individuals resting both at present and at the immediately previous time point, when at average levels of past fatigue and average levels of TH2/TH1, were expected to have a fatigue level of 0.9112, $t(88) = 5.86$, $p < .0001$. For resting individuals (i.e., the baseline category for the model) average in TH2/TH1 score (relative to the present sample) and average in past fatigue, for each point increase in past fatigue, there was a significant increase in present fatigue, $\beta = 0.68$, $t(2394) = 16.04$, $p < .0001$. Furthermore, positive scores for TH2/TH1, indicating a TH2 shift, were associated with greater current fatigue, $\beta = 0.02$, $t(2394) = 2.78$, $p = .006$. In addition, there was a significant amount of variability from person to person in momentary fatigue level, $\sigma = 0.02$, $SE = .01$, $Z = 3.41$, $p = .0003$.

Concurrent Activity

Overall, present activity was significantly related to present fatigue, $F(7,2394) = 11.36$, $p < .0001$. For all results, it is assumed that individuals were resting at prior time points and at average levels of predictors. Individuals who engaged in self-care [$\beta = -0.31$, $t(2394) = -6.33$, $p < .0001$], preparing or planning [$\beta = -0.18$, $t(2394) = -2.52$, $p = .01$], household activities [$\beta = -0.26$, $t(2394) = -5.30$, $p < .0001$], work [$\beta = -0.41$, $t(2394) = -7.65$, $p < .0001$], recreation or leisure [$\beta = -0.36$, $t(2394) = -7.79$, $p < .0001$], transportation [$\beta = -0.33$, $t(2394) = -6.18$, $p < .0001$] and treatment [$\beta = -0.29$, $t(2394) = -2.94$, $p = .003$] experienced significantly less concurrent fatigue than those individuals who were resting.

Lagged Activity

Overall, past activity was significantly related to present fatigue, $F(7,2394) = 3.89$, $p < .001$. Individuals engaged in preparation or planning at the previous time point experienced significantly more present fatigue than individuals who were resting at the previous time point $\beta = 0.79$, $t(2394) = 3.29$, $p = .001$. Among the remaining lagged activity categories (i.e., self-care, household activities, work, recreation or leisure, transportation, and treatment), no significant differences in fatigue were observed when compared to lagged resting.

Lagged Activity by Lagged Fatigue Interaction Effects

Overall, there was a significant past activity by past fatigue interaction, $F(7,2394) = 5.97$, $p < .0001$. Individuals engaged in preparation or planning in the past experienced a significantly weaker relationship between past fatigue and present fatigue than did individuals who were resting, $\beta = -0.20$, $t(2394) = -2.70$, $p = .007$. More specifically, individuals who were resting previously had an association of 0.68 (see above) between past fatigue and present fatigue, whereas individuals who were engaged in preparation or planning had a relationship of 0.48 (i.e., $0.68 - 0.20$). For those who were working previously, there was a significantly stronger relationship between past fatigue and present fatigue than those who were previously resting, $\beta = 0.11$, $t(2394) = 2.29$, $p = .02$. For each point of fatigue for individuals working, for one point increase in past fatigue, we expect a 0.79 (i.e., $0.68 + 0.11$) point increase in present fatigue. Individuals engaged in recreation or leisure in the past experienced a stronger relationship between past fatigue and present fatigue than individuals who were resting in the past, $\beta = 0.11$, $t(2394) = 2.28$, $p = .02$. For each point of fatigue for individuals engaged in past recreation or leisure, for one point increase in past fatigue, we expect a 0.79 point increase in present fatigue.

Discussion

Findings from this study suggest that current activity, a TH2 immune shift, past activity, and past fatigue can predict current fatigue among patients with CFS. In terms of current

activity, results showed that engaging in all activities predicted significantly lower fatigue compared to resting. In addition, a TH2 shift was related to higher levels of current fatigue. Furthermore, fatigue intensity 30 minutes prior as well as prior preparation or planning was associated with significantly higher fatigue intensity compared to resting.

An unexpected finding was that engaging in a variety of current activities was related to less current fatigue than resting. Those who were engaging in other activities possibly had more energy, whereas those who were resting during that 30 minute time period might have been doing so because they had higher fatigue. In addition, it is certainly understandable that higher prior levels of fatigue were related to higher current levels of fatigue. It appears that fatigue that occurs in the previous 30 minutes does have an impact on what people currently experience. It is also understandable that preparation and planning during the previous 30 minutes would be related to more current fatigue than resting, as preparation and planning might involve taxing activities for patients with CFS. However, it is unclear why preparation and planning would have this significant effect but not other activities.

Past preparation or planning, working, and recreation or leisure were significant moderators of the relationship between past fatigue and current fatigue when compared to resting. For preparation or planning, the estimate was negative, indicating a weaker influence of preparation or planning on the relationship of past and present fatigue compared to resting. This appears to contradict the earlier findings, and suggests that these relationships are complex, and more work needs to occur to understand these dynamics. If participants had higher fatigue when resting, then this possibly influenced the prior levels of fatigue and current fatigue more than preparation or planning. However, for working and recreation or leisure, the estimate is positive, indicating a stronger influence of recreation or leisure and working on the relationship of past and present fatigue compared to resting. Perhaps when working and involved in recreation or leisure, individuals exerted more energy, and this ultimately influenced the stronger relationship between prior and current fatigue.

Findings regarding the TH2 shift suggested that those with more impairment to the immune system experienced higher levels of fatigue. Van Houdenhove, Van Den Eede, and Luyten (2009) suggest that at an early stage of the illness, a switch takes place from HPA axis hyper- to hypofunctioning, and this observation is supported by some animal and human data. When the HPA axis becomes downregulated, there is still not an effective TH1 response to attack viral infections, however, now the immune system may cause inflammation (explaining elevated antinuclear antibody levels). Clauw and Chrousos (1997) suggest that individuals who develop CFS may be genetically predisposed to development of the condition, and that hormonal changes in people with CFS are primary, while immune changes are secondary. In a review article, Van Den Eede, Moorkens, Van Houdenhove, Cosyns, and Claes (2007) concluded that even if the HPA axis dysfunction is not the primary factor, it is probably a relevant factor in CFS symptom propagation. In the present study, the link between TH2 shift and fatigue provides more evidence of the possible role of immune dysregulation among patients with CFS.

Results from this study have implications for the management of CFS fatigue symptomatology. Stress reduction is an important component of symptom improvement among patients with CFS (LeRoy et al., 1996), and has been a focus of non-pharmacological interventions for the illness (Jason et al., 2007). As illustrated in the present study, there is a relationship between types of activity and rest, and their effects on fatigue. For example, it is easy to assume that resting should result in lower fatigue compared to engaging in other activities, and while this might be the case over an entire day, for shorter time intervals, rest might very well be associated with more fatigue, as was found in the present study. In addition, higher previous fatigue levels seem related to higher later fatigue levels. Finally,

the type of activity one engages in might have moderating effects on the relationship between earlier and later fatigue, with some activities increasing the strength of this relationship and other activities decreasing the strength of this relationship. This finding is consistent with the energy envelope theory as it is possible that experiencing higher levels of previous fatigue while engaging in work or recreation or leisure could result in increased subsequent fatigue. A correlational study found that individuals with ME/CFS experience a range of negative symptoms and disability when they extend beyond their energy envelope (Jason, Muldowney & Torres-Harding, 2008). We certainly need to know more about these complex interactions between the activity engaged in and the experience of fatigue.

There were several limitations in the study. First, some of the self-report measures might have some overlap, and this could have affected the outcomes. Data were from only one sample of patients, and these findings therefore need to be replicated with other samples. There also might be different subtypes of patients within this sample, and clearly larger samples are needed to help understand the role of fatigue and activities among subtypes. Finally, longer term data collection is needed to ascertain the effects of fatigue and activity over longer periods of time. Certainly more research is needed, but this study does suggest that activity logs can provide investigators and clinicians with valuable sources of data for understanding patterns of behavior and activity among patients with CFS.

Acknowledgments

The authors appreciate the financial assistance provided by the National Institute of Allergy and Infectious Diseases (grant number AI49720).

References

1. Antoni, MH.; Fletcher, MA.; Weiss, D.; Maher, K.; Siegel, BS.; Klimas, N. Impaired natural and heightened lymphocyte activation relate to greater disruptions in patients with CFS. Poster presented at the Sixth International Conference on Chronic Fatigue Syndrome, Fibromyalgia, and Related Illnesses; Chantilly, Virginia; 2003 Feb.
2. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation*. 1997; 4:134–153. [PubMed: 9500148]
3. Cooper L. Report of survey members of local ME groups. 2000 Nov 11. Retrieved from <http://www.afme.org.uk/res/img/resources/Group%20Survey%20Lesley%20Cooper.pdf>.
4. Friedberg F, Sohl SJ. Longitudinal change in chronic fatigue syndrome: What home-based assessments reveal. *Journal of Behavioral Medicine*. 2009; 32:209–218. [PubMed: 19101789]
5. Hawk C, Jason LA, Pena J. Variables that differentiate chronic fatigue syndrome from depression. *Journal of Human Behavior in the Social Environment*. 2007; 16:1–14.
6. Hawk C, Jason LA, Torres-Harding S. Reliability of a chronic fatigue syndrome questionnaire. *Journal of Chronic Fatigue Syndrome*. 2007; 13:41–66.
7. Jason LA, Brown M. Sub-typing daily fatigue progression in chronic fatigue syndrome. 2011 Paper submitted for publication.
8. Jason LA, Melrose H, Lerman A, Burroughs V, Lewis K, King CP, et al. Managing chronic fatigue syndrome: Overview and case study. *AAOHN Journal*. 1999; 47:17–21. [PubMed: 10205371]
9. Jason LA, Muldowney K, Torres-Harding S. The energy envelope theory and Myalgic Encephalomyelitis/chronic fatigue syndrome. *AAOHN Journal*. 2008; 56:189–195. PMID: 18578185. [PubMed: 18578185]
10. Jason LA, Timpo P, Porter N, Herrington J, Brown M, Torres-Harding S, et al. Activity logs as a measure of daily activity among patients with chronic fatigue syndrome. *Journal of Mental Health*. 2009; 18:549–556.

11. Jason LA, Tryon W, Frankenberry E, King C. Chronic Fatigue Syndrome: Relationships of self-ratings and actigraphy. *Psychological Reports*. 1997; 81:1223–1226. PMID: 9461755. [PubMed: 9461755]
12. Jason LA, Tryon WW, Taylor RR, King C, Frankenberry EL, Jordan KM. Monitoring and assessing symptoms of chronic fatigue syndrome: Use of time series regression. *Psychological Reports*. 1999; 85:121–130. PMID: 10575979. [PubMed: 10575979]
13. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*. 2004; 130:601–630. [PubMed: 15250815]
14. Skowera A, Cleare A, Blair D, Bevis L, Wessely SC, Peakman M. High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. *Clinical & Experimental Immunology*. 2004; 135:294–302. [PubMed: 14738459]
15. Stone AA, Broderick JE, Porter LS, Krupp L, Gnys M, Paty JA, et al. Fatigue and mood in chronic fatigue syndrome patients: Results of a momentary assessment protocol examining fatigue and mood levels and diurnal patterns. *Annals of Behavioral Medicine*. 1994; 16:228–234.
16. Tryon WW, Jason LA, Frankenberry E, Torres-Harding S. Chronic fatigue syndrome impairs circadian rhythm of activity level. *Physiology & Behavior*. 2004; 82(5):849–853. PMID: 15451649. [PubMed: 15451649]
17. Van Den Eede F, Moorkens G, Van Houdenhove B, Cosyns P, Claes SJ. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. *Neuropsychobiology*. 2007; 55(2):112–120. [PubMed: 17596739]
18. Van Houdenhove BV, Van Den Eede F, Luyten P. Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a ‘crash’ in the stress system? *Medical Hypothesis*. 2009; 72(6):701–705.
19. van der Werf SP, Prins JB, Vercoulen JHMM, van der Meer JWM, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *Journal of Psychosomatic Research*. 2000; 49:373–379. [PubMed: 11164063]
20. Wood C, Magnello M, Sharpe M. Fluctuations in perceived energy and mood among patients with chronic fatigue syndrome. *Journal of the Royal Society of Medicine*. 1992; 85:195–198. [PubMed: 1290537]