The Importance of Fatigue in Lupus

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Presented at the BC Lupus Society Symposium on November 3, 2007

Fatigue is a very common problem that has been ignored because we as rheumatologists, and you as patients, are often more concerned about other major (organ) involvements than worrying about fatigue. But fatigue is a very important component from the overall symptoms that patients suffer.

Prevalence of fatigue in SLE

Research has shown that fatigue will affect 80-100% of patients with SLE. As a presenting symptom, it is an important clue in making a diagnosis as it is the most frequent symptom in SLE. Fatigue is present in 80-90% at disease onset. In 30-50% of lupus patients fatigue is the most debilitating symptom interfering with physical, social and emotional functions. However, it is usually assumed as "benign" in the context of other lupus manifestations and there is often nothing that the physician can offer. Very often you, the patient, are more concerned about other manifestations from your disease than fatigue.

Factors associated with fatigue in SLE

The cause of fatigue is unknown but there are several factors that contribute to fatigue. Fatigue is an important component of other diseases, i.e. cancer, diabetes and especially chronic disorders. Is there an association between fatigue and disease activity? Some people believe there is and some people believe there is not.

First, we need to understand what it means in research to say there is a correlation. Correlation values vary between zero to one. A "0" means there is no correlation (factors are independent and have no relationship) and "1" means there is 100% correlation (if one factor changes then the second factor will also change in the same proportion and direction). For example a correlation of .5 means that if one factor is changed then a 50% change will occur in the second factor.

To determine the best way to measure fatigue, Dr. Matthew Liang organized through the American College of Rheumatology, an ad hoc committee to develop a systematic review on measuring fatigue. As co-chair of the ad hoc committee I am presenting the data today and this paper will be published in December.

We identified 34 studies that have been published in the last 40 years. Ten of these studies evaluated correlations between fatigue and disease activity. Eight studies found a significant correlation with a range between 0.26 and 0.53. There were many different instruments to measure disease activity in these studies, i.e. SLAM, SLEDAI, ECLAM, DAI. The SLAM is the most sensitive and the only instrument that showed a positive correlation between fatigue and disease activity. This suggests that disease activity is correlated to fatigue but the correlation depends on what instrument is used to measure disease activity.

Nine of these 34 studies evaluated the association between fatigue and depression. Eight studies found a significant correlation between the two (0.22 - 0.61). This means that if you get more depressed you will have more fatigue. Again, the range in correlations is due to the instruments used to measure depression.

Four of the 34 studies evaluated the association between fatigue and pain. Three studies found significant correlations (0.47 - 0.74).

Four studies evaluated the association between fatigue and sleep and two found significant correlation (0.46 - 0.47).

Only one study evaluated the relationship between fatigue and anemia. There was no significant correlation (-0.24). You can see here a negative sign. A negative correlation means that they are negatively correlated. In other words the two variables will go in opposite directions. Thus, if one factor increases its value the other factor will decrease its values.

How to measure fatigue?

We did a search on how many studies have been published about fatigue in general. There were less than 25 from 1975-1979 and over 900 from 2000-2004. Eighty percent were published in the last decade. Altogether there were 2,285 papers on fatigue using 252 different ways of measuring fatigue. One hundred and fifty of these instruments were only used once; 156 were multi-symptom scales, meaning they used fatigue as only one of many measured symptoms (non specific for fatigue). Seventy-one instruments were developed specifically to measure fatigue. Many were designed for specific diseases, including lupus.

As I mentioned, an ad hoc committee on SLE response criteria for fatigue was formed to perform a systematic review on the measurement of fatigue in SLE. We wanted to answer these questions: Do we have valid and reliable instruments available? Do we need another instrument to measure fatigue in lupus? How have we been measuring fatigue in SLE in the last 30 years?

We searched MEDLINE and EMBASE databases, as well as clinical experts, and books from 1966 to 2006. We evaluated the psychometric properties of each instrument. This is an advanced way of measuring if an instrument really measures what it's supposed to measure, its reliability, its ability to discriminate (fatigue from non fatigue) and its ability to respond to change.

The whole process happened in three steps: First a working group summarized the existing literature; this group presented to a larger panel of experts who met in Germany and who then presented to a larger expert panel. Many of the people who have been doing lupus research were involved. It was very important for the group to evaluate responsiveness of the instruments (i.e., be able to detect change in fatigue levels after treatment).

We identified 15 fatigue instruments that were used in the 34 studies. I will focus on instruments that have been used specifically in lupus patients:

1. FSS (Fatigue Severity Scale) was developed for patients with Multiple Sclerosis and lupus. This instrument was used in 19 studies. This was the most frequently used instrument.

2. MAC-FS – developed by Dr. Matthew Liang for a clinical trial in 1995 was used in 3 studies.
3. FAI, a version of FSS, is a multi-dimensional scale (measures fatigue in different dimensions, i.e. mental fatigue, physical fatigue, depression associated fatigue, etc) was used in 1 study.
4. SBPI (The Sjogren Based Psychometric Instrument) was also used in 1 study.
Remember that we set responsiveness as an important criterion for the evaluation of fatigue instruments (ability to detect change in fatigue levels). Only three of the 34 instruments evaluated had been tested for responsiveness in SLE: These instruments were FSS, MAC-FS, and MFI-20. The FSS has been translated to French, Spanish, German, Portuguese and Chinese, suggesting a great acceptance in the world. This also allows comparison of fatigue levels across different countries since they are using the same instrument. This instrument was the only one that tested for correlation for disease activity, depression, pain, sleep disorders and anemia.

Impact of fatigue on quality of life
The SF-36 is an instrument used to measure quality of life in many dimensions including general health, bodily pain, vitality, physical functioning, mental functioning, social functioning, and physical and emotional roles. FSS (fatigue severity scale) had a good correlation with all dimensions measured by the SF-36.

Management of fatigue in SLE
Only six studies in the last 40 years (290 patients) world-wide have looked at treatment for fatigue. Not a single study evaluated drug treatment for fatigue. One study evaluated group self-management that included a two hour session per week per six weeks. This study showed improvement using this technique. Four studies measured the effect of exercise on fatigue. There has been scientific evidence to support that exercise helps with fatigue. Two of the studies showed improvement. All four studies used a randomized control trial, which is the best way to show if a therapy works. The last study used telephone counseling, and this was also some benefit.

Some of these studies used more than one instrument to measure fatigue.

Future directions for fatigue in SLE
We still need to identify the most important contributors for fatigue in lupus, i.e. depression, pain, sleep disorders, disease activity as well as other non studied contributors including gender, age, culture, and disease duration on a patient's perception of fatigue. We also need to address other dimensions of fatigue. Also the impact of medications on fatigue has not been evaluated properly (Does prednisone improve fatigue?). Since there is no gold standard to measure fatigue in lupus, the committee decided to recommend the use of FSS to measure fatigue and we hope that future clinical trials will use this instrument. We also need to include patient's perspective on fatigue. Thus, how much improvement does a patient need to feel before we can say that treatment worked? A recent study from our group found that a 10% change in the FSS will be considered significant from the patient's perspective. This study needs further confirmation by other scientists.

Conclusion
Fatigue is the most prevalent symptom in lupus. Up to 50% of people with lupus feel it is the most disabling symptom. Fatigue correlates with depression, sleep disorders, and pain. It also

correlates with disease activity only if the SLAM is used to measure disease activity. Fatigue measured with the FSS correlates with quality of life. No pharmacologic therapies have been evaluated for fatigue. Exercise and psychosocial interventions seem to be effective in the management of fatigue.

We suggest that the FSS is the best available instrument to measure fatigue in SLE in future studies based on its validated psychometric properties, the fact that it is the most commonly used instrument until today, and it has been used and validated in several languages. Future research areas of interest are longitudinal studies of fatigue in early lupus, identification of clinical and psychosocial factors as determinants of fatigue in diverse patient populations.

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