

Dr. Lapp's presentation in Japan, November 4, 2012

I have come to talk to you today about Persons with CFS.

The worldwide prevalence of CFS/ME is about 400 cases per 100,000 (but up to 300 cases per 100,000 in Japan). This means that up to 400,000 Japanese people may suffer with this illness. This incidence makes CFS much more prevalent than Rheumatoid Arthritis, Multiple Sclerosis, or even breast cancer. CFS/ME is reported worldwide, and recognized as "real" by the WHO and many eminent medical associations; however, CFS/ME is still regarded by some a (1) a wastebasket term or (2) just depression.

Based on Japanese studies, from 300,000 to 400,000 Japanese people awaken every day with symptoms of influenza, aching, foggy thinking, and exhaustion after minimal activities such as bathing, dressing, or fixing a meal. They do not sleep soundly and they do not awaken feeling refreshed. They may have daily sore throats, swollen lymph glands, and headache. Many experience excessive sensitivity to light, sound, temperature, odors, and medications. They may be overly vigilant due to an overactive sympathetic nervous system. As a result they are nervous and anxious like an animal that has been frightened, and frightened, and frightened over and over.

It is no surprise that such individuals would present with 20 or more symptoms. They are complex and very challenging. But they are like a person who is drowning, and it is the job of the physician to throw them a life preserver. Such individuals also impose a tremendous economic burden on the Japanese nation. Based on data from the United States, this illness could account for \$180 million (14 billion Yen) in total healthcare expenditures in Japan, and \$0.5 billion (37 billion Yen) of lost productivity (Lin J, Cost Eff Resour Alloc. 2011).

I am going to focus today on 5 areas: (1) the signs and symptoms of CFS; (2) the evidence that CFS is a real illness; (3) the evidence that CFS is not due to depression; (4) the American approach to management; and (5) Pediatric CFS. My approach to managing CFS may differ significantly from the approach taken in Japan, but it is my humble hope that the treatments we have found effective in the United States will be of great benefit to you in Japan. And I hope that my presentation will not only provide a framework for CFS sufferers to follow, but that Japanese physicians will also benefit from this approach.

2. Brain Abnormalities

MRI Scans show high intensity white spots in 80% of cases. SPECT Scans show decreased blood flow in specific areas of the brain, especially the midbrain and temporal lobes. Neuro-psychiatric testing confirms problems with attention, memory, and processing speed.

3. Autonomic Nervous System

Abnormalities of the sympathetic and parasympathetic nervous system are common, including tachycardia (or fast heart rate), orthostatic intolerance (fainting) in up to 100% of subjects, and low plasma volume and red blood cell mass. Patients tend to have rapid heart rate, low blood pressure, and syncope (fainting).

4. Sleep Disruption

Sleep is markedly disturbed in up to 62.5% of patients. Evaluation in the sleep laboratory frequently reveals sleep apnea, sleep walking, narcolepsy or upper airway resistance.

5. HPA Axis

Abnormalities of the mid-brain cause suppression of the hypothalamus. This in turn suppresses the

pituitary. Suppression of the pituitary leads to diminished function in the endocrine glands, including the thyroid, adrenal gland, and gonads (sexual glands). Thus, many patients have low cortisol and DHEA, low thyroid, and sexual dysfunction such as early menopause and loss of libido.

6. Immune System

The immune system is affected in CFS. This is manifested by “cytotoxic” T cells, poorly functioning natural killer cells, upregulation of the anti-viral enzyme RNaseL, increased inflammatory cytokines, and reduced levels of antibodies. As a result we can see reactivation of old viral infections, auto-antibodies, inability to fend off viral and fungal infections, recurrent Staphylococcal and Streptococcal infections, influenza symptoms, and fevers.

7. Genetics

Twin studies and the study of family histories has demonstrated that these Human Leukocyte Antigens are inherited, and that the risk of a descendant developing CFS ranges from 2.7 times normal for children, 2 times normal for more distant relatives. Several gene variants that are present in persons with CFS control neurotransmitters (brain chemicals) that control tryptophan (TPH2), serotonin (COMT), and glucocorticoids (NR3C1). These genes control mood, sleep, motivation, pain, body development, and metabolism, which explains many of the symptoms that we see in persons with CFS.

8. Oxidative Stress / Energy Metabolism

Oxidative stress is increased in persons with CFS as measured by an increase in low density lipoprotein (LDL) and the most reliable marker of free radical accumulation, F2 isoprostanes. Cellular energy – as measured by ATP – is reduced in persons with CFS. This may explain why persons with CFS have very low energy levels, poor stamina, and malaise after minimal exertion.

9. Gene Expression of mRNA

These graphs demonstrate that moderate exercise increases mRNA expression for sensory, adrenergic, and immune genes in CFS patients but not in normal subjects. Dr. Light at the University of Utah measured the production of mRNA by genes in controls and patients. Each color represents a different mRNA and each cluster represents a period of time after modest exercise on a stationary bicycle. You can see clusters of data for 30 minutes, then 8, 24, and 48 hours after exercise. It is clear that persons with CFS (in the lower graph) produce more mRNA in response to exercise than the controls in the upper graph. Using these gene expression studies it is possible to distinguish normal individuals from persons with CFS; discriminate CFS from FM; determine the severity of the CFS; and even predict who will have orthostatic intolerance. This technology shows real promise as a marker for persons with ME/CFS or FM.

11. Gene expression tracks the severity of CFS

12. Post-Infectious CFS

75-85% of cases occur abruptly following a viral or flu-like illness. Two studies validate that common infections can trigger CFS. In 2006 and Australian study followed individuals who contracted mononucleosis (EBV), Q-Fever, and Ross River Fever. While most recovered from these illnesses, at one year 11% of patients met criteria for CFS. CFS did not develop more frequently in persons with a history of psychiatric illness, which suggests again that depression occurs as a result of CFS, and does not cause CFS. A more recent study followed over 300 adolescents who contracted mononucleosis. At 12 months 7% of patients met criteria for CFS – which is consistent with the Dubbo Study -- and at 24 months 4% of children still met CFS criteria.

13. Myth

Next I would like to dispel the myth that CFS/ME is caused by depression. Epidemiology, symptoms,

course of illness, and medical fact all support that CFS/ME is not caused by or due to depression.

14. Depression versus CFS/ME : Onset

First, depression usually develops insidiously, while 75-85% of CFS cases occur abruptly.

15. Depression versus CFS/ME : Epidemiology

CFS occasionally occurs in clusters or populations of patients. Small epidemics have been reported in England, the United States, Iceland, New Zealand, and many areas throughout the world. Depression occurs in individuals.

16. Depression versus CFS/ME : Medical Therapy

Antidepressants can significantly improve depression, but are seldom helpful in CFS.

17. Depression versus CFS/ME : Exercise

Likewise, exercise improves depression, but it worsens CFS. We will talk more about this later.

18. Depression versus CFS/ME : Symptoms

Many symptoms of CFS overlap with those of depression – particularly sleepiness, fatigue, and discomfort or pain. These symptoms are much more severe in CFS, however. And some symptoms, such as fever, headache, and post-exertional malaise are common in CFS but are not typical of depression.

19. Depression versus CFS/ME : Outlook

Perhaps the most obvious distinction between depression and CFS is that depressed persons are hopeless, helpless and withdrawn. On the other hand, persons with CFS tend to be very proactive, they seek medical treatment, and they tend to be politically active – like all of YOU!

20. Biological Evidence Against Depression

Biological evidence against depression as a cause for CFS can be found in the HPA Axis. The hypothalamus controls the pituitary, and the pituitary controls the endocrine glands. When adrenal function is studied, cortisol is elevated in persons with depression due to elevated CRH from the pituitary. CFS is just the opposite: serum cortisol production is reduced due to a deficiency of pituitary CRH.

21. Four Cardinal Symptoms of CFS

Let us turn now to the symptoms and management of CFS. There are no tests that diagnose CFS, so we must rely upon symptoms (or a clinical case definition). The four core (or cardinal) symptoms of CFS are pain, trouble with thinking, fatigue, and non-restorative sleep. By non-restorative sleep I mean that sleep is very shallow and no matter how much sleep a patient gets, she will still awaken feeling very tired, stiff, and foggy.

22. Overlaps Syndromes

In addition to the four core symptoms, persons with CFS are 7 to 9 times more likely to have comorbidities or overlap syndromes. The most common overlap syndromes are irritable bowel, irritable bladder, migraine, dry eyes and mouth (Sjögren 's syndrome), sacro-iliac (low back) pain, etc.

Epidemiology

From an epidemiological standpoint there is no known cause for CFS, but triggers have been identified. In about 85% of cases the trigger is a viral or flu-like infection. Long term studies in the United States show that a majority of persons with CFS improve over time, usually months to years. However,

23. CFS/ME Triangle

To help understand CFS, I frequently refer to the CFS Triangle: Sleep – Pain – Fatigue. These three symptoms are all interrelated. For example, if you have pain it is difficult to sleep and pain is exhausting or fatiguing. There are few treatments for fatigue, but pain and sleep are eminently treatable. Fatigue (and cognition) tend to improve when sleep and pain are addressed.

24. Managing Sleep Problems

To manage sleep, it is first important to have good sleep habits. For example:

- Use the bed only for sleeping

- Go to bed when sleepy; never try to make yourself sleep

- Hide the clock from view (so that the time of night does not cause anxiety)

- Don't be afraid of insomnia; quiet rest is almost as good as sleep

- Keep a regular schedule. Set an alarm and get up at the same time every morning.

When good sleep habits alone are not sufficient, then simple sleep aids might be helpful, such as melatonin or an antihistamine. The next step would be to add a patented sleep medication such as eszopiclone, zaleplon, ramelteon, or zolpidem. If sleep is not improved with these simple therapies, it is important to consult a sleep specialist because severe sleep disorders occur in up to 62.5% of persons with CFS (compared to 7% in the general population).

25. Managing Pain

Pain can be managed with medications or non-pharmacological therapies. Non-pharmacological therapies include rest, cold, heat, mineral baths, liniments, massage and physical therapies. Pharmacological therapy begins with over-the-counter medications such as acetaminophen, aspirin, and ibuprofen. In the United States, three medications have been approved for the neuropathic pain of CFS. These are pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella). These reduce pain modestly, but may have side effects such as nausea, sleepiness, and dizziness. Acute pain or severe pain may need to be addressed with narcotic medications (such as tramadol, hydrocodone, oxycodone, or morphine), although we try to avoid such medications because of possible addiction and side effects such as drowsiness, hearing loss, and infertility.

26. 4 CFS Characteristics

In addition to the Four Core Symptoms CFS is accompanied by four typical characteristics:

First, CFS is an exertional illness. If you exert too much you get ill; on the other hand, if you rest too much you will get stiff, sore, and deconditioned. So the lesson here is that it is important to “stay active but not too active.”

Second, CFS is positional. That is, the illness gets worse with standing, but is relieved by lying down. The lesson here is that lying down frequently is very important.

Third, persons with CFS have unique sensitivities. They become sensitive to light, sound, the chemicals, odors and fumes; and the temperature must be just right! If you get too cold you will suffer severe shivering; if you get too hot you will feel weak and maybe even faint.

Last, persons with CFS do not tolerate any stress. “Stress” may include deadline or appointments, confrontation with family or friends, even difficulty with paperwork or dealing with government regulations. It is important to know that mental stress (like reading, concentrating, or using the computer) is exhausting also, so it is important to take frequent breaks from such activities. I recommend a rest period after 30-45 minutes of such activities.

27. Pacing

This is perhaps the most important concept that I can report to you: **it is important to rest frequently and set limits on activity**. Please consider taking at least 2-3 rest periods each day. Usually 10-30 minutes is sufficient, but because the positional sensitivity you must recline; and due to stress intolerance you must clear your mind. In other words, do not read, make plans, watch television, talk on the telephone while attempting to rest.

You might hear from some sources -- including your own doctor -- that it is important to exercise aggressively. Actually scientific evidence has shown that too much exertion will actually make your symptoms worse. Most persons with CFS tend to “push and crash.” That is, they exert too much then are exhausted for hours to days afterward. Persons who “push and crash” regularly **will not get better** because the body never has an opportunity to recover. The key to improvement is “energy conservation.” That is, find out what are the limits of your energy and then stay within those limits. Once again, it is important to “**stay active but not too active.**” In order to accomplish this you may need help from family and friends; or you may need to delegate work such as housekeeping or cooking; and you may have to lower your expectations for keeping house, working, or exercising.

28. The Fallacy of Pushing and Crashing

This slide illustrates the fallacy of pushing and crashing. Let us suppose that you have ten blocks of energy to use over 4 days. Here is one block. If you exert too much for a day or two, then there is little energy left for the next two days. So you may be very active for two days but then must recuperate for two days. This type of activity is common, but prevents improvement from CFS. On the other hand, if you moderate activity for the first two days, then you still have energy for the next two days. You can accomplish more with this approach!

29. Activity

Resting all the time is just as bad as pushing and crashing. No one ever gets better from lying around all the time. Once again, despite what you may hear from other sources even the sickest patient can do some activity, and it is important to attempt some activity if you expect to improve. Studies have shown that even CFS patients in wheelchairs can exercise **as long as they do not over-exert**. That leads to the question, how much exertion is too much. Exercise studies in our laboratory and elsewhere have demonstrated at least three ways to set objective limits on your exertion: interval activity, limiting your heart rate, and limiting the number of steps taken per day.

30. Anaerobic Interval Activity

Using a technology called Cardiopulmonary Exercise Testing we are able to better understand why persons with CFS have low energy, reduced stamina, and malaise after exertion. One of the first lessons we learned was that persons with CFS cannot tolerate anaerobic activity. “Anaerobic” means that not enough oxygen gets to muscles. The muscles then must use glucose instead of oxygen as a source of energy, and glucose metabolism produces toxic products such as lactic acid. Most persons with CFS can only exert 3-5 minutes before reaching this Anaerobic Threshold ; then they must rest for 5 minutes in order to recover. Therefore it is possible to reduce flares and relapses by exerting for only 3-5 minutes at a time, followed by 5 minutes of rest. We call this Interval Activity. The problem with Interval Activity is that most people prefer NOT to vacuum, mow, or exercise in short intervals. They like to keep going ...

31. Heart Rate Limits

The second lesson that we learned was that the Anaerobic Threshold always occurs at the same heart rate. Applying this principle, we can prevent relapses by limiting exertion so that the heart rate never exceeds this level. Cardiopulmonary Exercise Testing helps us determine the heart rate at the Anaerobic Threshold. We can estimate this maximum heart rate, however, by using the formula shown here. A person’s maximum predicted heart rate is equal to 230 minus the age in years. For a 50 year old individual, then, the Maximum Predicted Heart Rate is 230 minus 50, or 180 beats per minute. The heart rate at the Anaerobic Threshold is 60% of the Maximum Predicted Heart Rate. So 180 multiplied by 0.6 equals 108 beats per minute. With this number in mind, you can purchase an inexpensive heart monitor to insure that you do not exceed this limit.

32. Pedometer (Steps Per Day)

One last way to limit exertion is by monitoring steps per day. Just obtain an inexpensive pedometer and wear it all day. We know from experience that 1000 steps per day is too little activity and will lead to stiffness, soreness, and deconditioning. 5000 steps per day is too much for most, and could trigger a flare or relapse.

33. Severely Affected Patients

Please keep in mind: so far I have been making recommendations for persons with moderate symptoms of CFS. I understand, however, that many Japanese patients are severely affected. They are mostly house bound, sometimes chair or bed bound. They experience considerable difficulty with all aspects of personal care and may need help with even meal planning and preparation. Many are incapable of living independently. In addition, they are more likely to suffer food and chemical sensitivities, and may be extremely sensitive to light, sound, and temperature. Some have severe neurological symptoms such as atypical seizures, swallowing or speech difficulties, muscular jerking, or profound weakness. We do not know why some patients are more severely affected than others. Many can be rehabilitated but it takes special effort such as:

- Home visits from the doctor or specialist (or telephone consultations)
- Occupational therapy to improve the home environment (e.g., assistive devices, walkers, special computer stands, ergonomic beds)
- Home physical therapy (range of motion or resistance against gravity, supine)
It is important for these individuals to stay active also, although the limitations are greater
- Home Health Aid or caregiver (for cooking, laundry, housekeeping, shopping)
Patients should be provided with balanced nutrition and healthy organic or whole foods
- Insure pleasant activities (such as writing, embroidery or knitting, watching nature, music, books on CD)
- Insure socialization (such as brief visits from friends or family, Facebook or other social media)

34. Severely Ill Patients

- Due to sensitivities, minimize medications and supplements to those absolutely necessary
- Prescribe medications in *very low* doses and titrate slowly
- Stress management and grief/loss counseling can be extremely helpful
- Encouragement. Try to achieve something every day; and do not accept your current restrictions. (Aim to improve 1% each week!)
- Have lowered expectations for themselves and from others
- Above all the severely ill need “peace of mind and a feeling that they and their family were taken care of, so that they could use all their energy on getting better.”

35. Pediatric CFS/ME : Epidemiology

Another topic that is infrequently discussed is CFS/ME in children and adolescents. While CFS/ME is common in adults, it is much less prevalent in children and adolescents. One very large survey in Chicago (USA) identified NO children with CFS/ME under the age of 12. On the other hand, the prevalence in adolescents (age 13-17 years) was 181 per 100,000. Overall, the prevalence of pediatric CFS/ME in the United States is estimated at 100 to 300 cases per 100,000 persons. Takako Johdoi reported in 2009 that the Japanese prevalence was “about the same” as in the United States. As in adults, a predominance of females are involved, with ratios of two to five females for each male with the disorder.

36. Comparison of Symptoms in Adolescents and Adults

Adolescents and adults have similar core CFS/ME symptoms, such as pain, fatigue, cognitive difficulties, and non-restorative sleep. However, adolescents are much more likely to complain of abdominal pain, sore throat, photophobia (or eye pain), swollen glands, and rashes.

37. Differences Between Adolescent and Adult Definitions

- De-emphasizes fatigue and highlights symptoms(dizziness, decreased endurance, pain, & flu-like)
- Symptoms endured for only three months
- Abdominal symptoms have been added to list
- Autonomic symptoms added(orthostatic intolerance, palpitations, dizziness, shortness of breath)
- Symptoms rated according to severity
 - 1 = not present
 - 4 = moderate
 - 7 = severe
- Symptoms must be either moderate to severe to meet criteria

38. Pediatric CFS/ME Management

The management of pediatric CFS/ME is similar to that of adults: sleep and pain are addressed first, then comorbidities such as orthostatic intolerance and abdominal issues. Additionally, in children it is necessary to assure that education is continued (sometimes by means of home instruction, tutoring, or a shortened school curriculum. Because children may not be able to attend school and make friends, outside activities and social development needs to be addressed also. Lastly, a Japanese study showed that 36% of school phobia cases were attributed to CFS/ME, confirming that CFS/ME takes a psychological toll on adolescents.

39. Prognosis in Adolescents(15 Year Follow-Up)

A longitudinal 15 year study by my associate, Dr. David Bell, demonstrated that the prognosis for adolescent CFS/ME is much better than adults, with almost 80% of subjects having recovered or improved significantly. 20% remained ill or very ill. Similar studies in the US and UK have shown similar improvement rates.

40. Summary of Pediatric CFS/ME

Another topic that is infrequently discussed is CFS/ME in children and adolescents. While the incidence of CFS/ME is high in adults, it is almost unheard of in children under the age of 10, and estimates of prevalence range from 100 per 100,000 to 300 per 100,000 in adolescents aged 10-17. The core symptoms of CFS/ME are similar in adolescents and adults, but children tend to have more abdominal pain, orthostatic intolerance (such as Neurally Mediated Hypotension and Postural Tachycardia), sore throat, photophobia, and rashes. The diagnosis of Pediatric CFS is made clinically using a “case definition” that was published in 2008. Dr. Terahusa Miike and I were authors on that paper. Management is mostly symptomatic, addressing pain and sleep problems first, then orthostatic and gastrointestinal issues. Children frequently have difficulty maintaining their school work, and so the physician must also assure that education continues, that the child has social opportunities and matures naturally. School phobia is a common problem that needs to be considered in adolescents. Lastly, the prognosis is more favorable in adolescents than adults, with up to 80% reported significant improvement or recovery, and about 20% remaining ill after 15 years.

41. Supplements

Many patients ask me what supplements I recommend in the management of CFS. First let me say that supplements only optimize health, but they DO NOT treat CFS Left panel: I consider this group to be “essential supplements” Right upper panel: these are worthy considerations. Right lower panel: these supplements are frequently recommended for mitochondrial support and are strictly optional. Please minimize supplements. Not all supplements are safe, and many interfere with necessary medications.

42. Advanced Therapies

Some patients may benefit from more specific therapies. Orthostatic intolerance occurs in up to 50% of adults and most adolescents with CFS. It is usually characterized by low blood pressure, rapid heart rates, and possible syncope (fainting). Treatment involves drinking lots of water and ingesting supplemental salt, but medications may be required. Many persons with CFS report diet sensitivities. Most common are sensitivities to gluten (wheat, barley, and rye) and dairy products. Many patients need to avoid aspartame and monosodium glutamate also. Antiviral medications may be indicated when laboratory studies demonstrate reactivation of viruses or there are immunological symptoms such as fever, sore throat, and swollen glands. Because the HPA Axis is suppressed, a subset of patients may benefit from supplementation of cortisol or growth hormone. Lastly, two experimental treatments for CFS that show great promise are Ampligen and rituximab. Both are immune modulators.

43. Summary

- Biological evidence for CFS is abundant
- CFS is not due to depression
- Begin management by addressing pain and sleep disorders first
- It is important to stay physically active, but not too active to trigger a flare

44. Summary (continued)

- Use interval activity, heart rate monitoring, or steps-per-day to prevent over-exertion
- The severely ill require additional care and resources, but can be rehabilitated
- Advanced therapy may benefit specific subsets of patients

Don't ever give up!

45. HUNTER-HOPKINS CENTER

This is our office in Charlotte, North Carolina. We occupy the top floor.