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Common symptoms and lumping chronic conditions together

In a lecture called "CFS Diagnosis: Are You a Lumper or a Splitter" co-sponsored by the Massachusetts CFIDS/ME & FM Association (MassCFIDS) and the Massachusetts Department of Public Health on April 28, 2012 Dr. Benjamin Natelson, Director of the Pain and Fatigue Center at Beth Israel Medical Center in New York City, presented twenty years of research and work with Chronic Fatigue Syndrome (CFS) patients. Dr. Natelson's wife, Dr. Gudrun Lange, Ph.D., a Clinical Neuropsychologist accompanied Dr. Natelson to Massachusetts, and in a surprise double-header, also spoke about the process of neuropsychological testing for CFS patients.

What's a syndrome?

Dr. Natelson explained that in CFS, as well as such other syndromes as Irritable Bowel Syndrome (IBS), Temporal Mandibular Joint Syndrome (TMJ), Migraine, Depression and Schizophrenia, there are common symptoms that seem similar and therefore, the medical professionals label it a syndrome. A syndrome is a cluster of symptoms that can have multiple causes. "We need to figure out ways to reduce the variability. CFS is the tip of the iceberg" he said. Fatigue can be related to many pain syndromes but whether the fatigue is a result of sleep problems or if the fatigue itself produces pain needs to be sorted out.

Fatigue most common symptom in medicine

There are many medical conditions and syndromes that are associated with severe fatigue. These conditions can include Chronic Fatigue Syndrome (CFS), Fibromyalgia (FM), Irritable Bowel Syndrome (IBS), heart failure, Multiple Sclerosis (MS) and Chronic Obstructive Pulmonary Disease (COPD). In fact, fatigue is the most common symptom in medicine, and there are multiple causes, including sleep disorders, infection or any number of other conditions. Dr. Natelson stressed that in CFS there is severe fatigue marked by a substantial decrease in activity.

Dr. Natelson presented statistics to drive his point home. A person has a 9% chance of

developing CFS within 6 months after a bad infection, but not necessarily lasting for more than 6 months. About 15% of breast cancer survivors fulfill the criteria for CFS. Fatigue is often the first symptom in Multiple Sclerosis (MS), and many Parkinson's patients are often debilitated by fatigue.

Lumper's approach

The lumper's approach groups all chronic conditions, such as CFS or FM, in which a person has physical symptoms that involve more than one part of the body but seemingly without physical cause, as a somatization disorder. Doctors are inclined to diagnose pain and fatigue related syndromes, which currently have no diagnostic test, as Somatic Amplification, a tendency to psychologically perceive normal sensations as overly intense.

Dr. Natelson feels that Somatic Amplification has a derogatory connotation and should be replaced with Medically Unexplained Symptoms. In fact, the rate of somatic disorder reported in CFS patients depends entirely on whether the cause of the symptoms is interpreted as psychological or physical by the physician who is making the diagnosis.

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Splitting patients into subgroups and looking for more ways to differentiate

The splitter's approach

When it comes to determining a cause for Chronic Fatigue Syndrome, is it better to lump CFS patients together with other chronic conditions causing pain and fatigue, or is it better to split patients into subgroups?

Dr. Natelson takes the splitter's approach and identifies patient subgroups in order to determine the cause, or causes, of Chronic Fatigue Syndrome. Dr. Natelson's research for biomarkers, a biological characteristic that can be objectively measured as an indicator of abnormal biological

processes, has pointed in the direction of a brain dysfunction in a specific subset of CFS patients. As there are most likely several causes for CFS, the subgroups help to narrow the pool of patients in order to determine specific causes. This process is called Stratification Strategy.

While FM is another way to split out a diagnosis, FM is tenfold more common than CFS because FM is a diagnosis that is made without any exclusions. CFS is a diagnosis of exclusion, which requires ruling out all possibilities causing fatigue such as thyroid disease, MS, Lupus, diabetes, etc. and hoping the fatigue will be resolved. The prevalence rate for FM is 3%, being mostly a women's health issue breaking down to 75% women to 25% men. The prevalence rate for CFS is 0.3% — again favoring women.

In a research paper Natelson published 10 years ago regarding sudden onset, it looks at CFS patients and charts the dates when they became ill. Looking at the chart shows the onset was not random because if random, the charted line would have been straight across. This line went up all around the same time, in winter, suggesting an infection-related trigger.

Stratification Strategy

Co-morbidity is the existence of another diagnosis along with CFS. Dr. Natelson looked at several ways of splitting CFS patients: CFS patients with and without Fibromyalgia; sudden or gradual onset of symptoms; severe or non-severe symptoms; cognitive impairment versus normal cognition; and patients with and without a psychiatric diagnosis—usually depression. About 35% of patients in Dr. Natelson's center reported a sudden onset of symptoms, while the balance report fatigue and symptoms that increased gradually.

Are CFS and FM the same?

In his clinical sample, Dr. Natelson compared CFS and FM to determine if they are the same condition. While overlaps do exist, there are medical differences as well. About 40% of the CFS patients fulfill the criteria for FM. About 20% of FM patients had CFS. The spinal fluid of FM patients shows an elevation of Substance P (responsible for pain), but that is not the case in CFS patients. Another study had shown that CFS was common in patients with obstructive sleep apnea, while FM was not. Also, FM pain responds to some anti-depressant medications, but CFS fatigue does not. Natelson concluded that CFS and FM are not the same and therefore do not have the same causes, nor should they have the same treatments.

Twenty years of research shows possible brain dysfunction

In the past twenty years, Dr. Natelson has conducted a number of studies to determine the differences, and possibly determine the causes, for CFS as compared to other syndromes, such as FM, Sjögren's and post-Lyme.

In a recently published study looking at sleep, CFS-only patients have increased rates of REM to wakefulness (tends toward awake) while CFS-plus-FM patients tend to fall asleep, but their sleep is disrupted by transitions to wakefulness. These marked differences may prove helpful in determining treatment approaches.

In a study looking at the blood prolactin (a hormonal surrogate for brain serotonin neuron activity) response to a tryptophan infusion, CFS patients showed increased brain response to the tryptophan infusion but not those with CFS-plus-FM or healthy controls. Studies done with depressed patients show an under-response to tryptophan infusion. His conclusion was that CFS and FM are not the same, as the lumpers believe, and patients may not respond in the same way to commonly prescribed treatments.

Natelson's hypothesis

Natelson's hypothesis is that some CFS patients, especially those that have no accompanying psychological disorders, have brain dysfunction or *encephalopathy*. Furthermore, Natelson believes that further study will identify biomarkers to accurately diagnose that subset of CFS patients.

In his first study, twenty years ago, Natelson compared the cognitive dysfunction in patients with CFS, MS and healthy patients. He found that CFS patients function worse than controls on timed complex attentional tasks, and that those with the most impairment could have an underlying encephalopathy, or brain dysfunction. As an example, he offered that a CFS patient in a quiet room talking to one person would be ok, but in a room with four people talking at once, the CFS patient would have a problem.

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Research, ongoing studies, and use of new technology

Research finding

He is now looking at the brain by studying spinal fluid - the fluid that bathes the brain - and using brain imaging techniques. *Brain MRIs showed more abnormalities in CFS subjects with no psychiatric disorder* as compared to CFS with a psychiatric disorder or to healthy controls. This finding again points to encephalopathy, especially in CFS patients without a coexisting psychiatric disorder. The study also found significantly more abnormalities in the frontal lobe of the brain, as well as a reduction of the brain blood flow than the other groups.

Spinal taps on forty-four CFS patients showed that 30% of those patients had spinal fluid outside the norm, including elevated protein and increased white blood cells. Again, there were more spinal fluid abnormalities in patients without psychiatric comorbidities and 27% of the normal spinal fluid patients had depression.

While one-third of CFS patients experience a sudden flu-like onset of symptoms, Dr. Natelson looked for viral infections while studying the spinal fluid and found no convincing data for persistent viral infections. Only a small fraction of patients had shown evidence of reactivated Epstein Barr Virus (EBV). He also found that Xenotropic Murine Leukemia Retrovirus (XMRV) was negative in the spinal fluid. Once an exciting possible cause for CFS, Natelson did not find the presence of the retrovirus in the spinal fluid. "That story is behind us," said Natelson.

He was also unsuccessful in replicating studies that showed immune activation, in which the immune system is turned on by a virus and then keeps running in CFS patients.

The search for biomarkers

Over time, reduced natural killer cells seem to be the only evidence of a reduced immune system that holds true across many studies. However, Natelson has found evidence for the opposite. While the pro-inflammatory cytokines make you feel sick, he has found evidence that

one of the anti-inflammatory cytokines, IL-10, was elevated and may contribute to disturbing sleep.

With today's technology, Dr. Natelson has come closer to finding biological abnormalities that could be used to unequivocally identify and diagnose Chronic Fatigue Syndrome in a specific subset of patients. Using MRIs to look at chemicals in the brain, Natelson compared Ventricular Lactate in CFS and controls as a possible biomarker. He found that CFS patients without a coexisting psychiatric disorder had higher lactate, and he has now replicated this study.

Natelson also believes that 15% of CFS patients have an autoimmune disorder that is being missed. He discussed Sjögren's Syndrome, another autoimmune illness, the main early symptoms of which are dry eyes and dry mouth but also include prolonged fatigue. A lip biopsy is the definitive way to diagnose Sjögren's, in which the body attacks its own tear and salivary glands. In his small study, all the patients had a negative result to Sjögren's antibody blood test, but about half of the 25 patients reported dry eyes and mouth. Then the tear production was measured and it was found 10 of those 13 patients had abnormal tear production. When lip biopsies were done on those patients, 1/3 were found to have an abnormal biopsy. Dr. Natelson thinks even though this was a small study, it may prove to be reliable in predicting autoimmune disease.

New technology

New technology now allows researchers to identify all the proteins in the spinal fluid. Through the use of mass spectrometry, an analyzer that separates proteins and breaks them down further and further than ever before, Natelson compared the proteins in spinal fluid between healthy controls, CFS patients and those with Post Lyme Fatigue Syndrome. There are 305 proteins common to both CFS and Post-Lyme disease. Natelson found 738 proteins unique to those with CFS. He is now working to identify three or four of those proteins that are specific to CFS to be used as a biomarker to diagnose at least a subset of CFS patients.

Findings so far

Some CFS patients have poorer neuropsychological test results, abnormal brain MRI imaging, poorer function in health related quality of life, wider reduction in brain blood flow, more

abnormal spinal fluid results, and higher levels of ventricular lactate, all which point to a brain disease.

Ongoing studies

Natelson is looking to better define the subgroup with a neurological cause and develop specific treatments and medications for them. In order to complete this new study, the National Institutes of Health (NIH) has awarded him a grant to repeat all of his past studies, including neuroimaging, neuropsychology and spinal taps, but all on the same group of patients.

There is also a new grant from the CDC to find out if the diagnosis of CFS is the same across centers. This has never been done. This study will compare how Dr. Natelson, a neurologist from NY, Dr. Nancy Klimas, an immunologist from Florida, and a leading CFS researcher/clinician, and another large group of practitioners expert in CFS make the CFS diagnosis.

There is a pharmaceutical industry study on using Milnacipran (brand name Savella) to see if it proves useful in reducing fibro-fog in FM patients. Milnacipran is a class of medications called selective serotonin and norepinephrine reuptake inhibitors. Colleagues of Dr. Natelson's from Cornell have just recently received notice that a study to try to improve brain chemistry with an available food supplement will be funded.

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Advice for treatment of chronic illness

Chronic illness treatment

Dr. Natelson's advice for treatment of any chronic illness has four components: education, medication, and two rehabilitative elements-very gentle physical conditioning and behavioral therapy, which can help the patient to learn new techniques to handle the illness. He stressed that this last technique is difficult to do on your own and best learned from a professional.

If patients are interested in joining the study, they will need to be off all medications that may alter brain chemistry or functioning. The study is also recruiting healthy controls and volunteers get a free work-up and are reimbursed for their time. The study is being conducted in New York City.

To participate in this momentous work, go to www.painandfatigue.com or call (212) 844-6747.

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