

The art and science of ME/CFS: A 2016 synopsis

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ME/CFS, a complex multisystem disease of diverse etiology, which results in significant functional and costly impairment, is estimated to affect approximately 40,000 Swedish residents. This synopsis describes developments by governmental agencies (i.e. the CDC); emerging clinical centers in Stockholm and Gothenburg, and the sophisticated Swedish research addressing basic and translational medicine, and physician education. A model is presented for Centers of Excellence, additional issues addressed: name change controversy, subsetting of patients, Big Data and Precision medicine, the microbiome, and current treatment challenges. Research obstacles and solutions are outlined including the profound lack of funding and attention afforded by government agencies, academic institutions, and pharmaceutical industry. Development of C.O.E.'s and optimism; based on new science and technology with worldwide collaboration, suggest hope for the future.

Myalgic Encephalomyelitis (ME/CFS) is a complex multi-system disease of probable diverse etiology and pathogenesis resulting in significant functional impairment. Significantly, the fatigue is generally worsened by physical or mental exertion. Common symptoms include cognitive dysfunction, autonomic manifestations of dysfunction, sleep abnormalities, pain, and GI complaints. Worldwide studies have indicated that when appropriately screened and diagnosed, the incidence rates are similar in the developed countries where it has been studied. A conservative estimate suggests that over 1 million Americans suffer from ME/CFS and further, that a significant proportion (>25%) are severely affected or disabled.

Current State of Affairs in the U.S. and Sweden

Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, is embarking on a collaborative innovative process in order to properly revise its educational materials. They have developed a Technical Development Work group (TDW) to identify the needs and priority topics for educational materials. The emphasis will be on evidence-based, understandable materials that are useful to all stakeholders. Hopefully, these reports and efforts will be available in translated form to interested parties including physicians, patients, and research organizations worldwide. The recent efforts by the National Institutes of

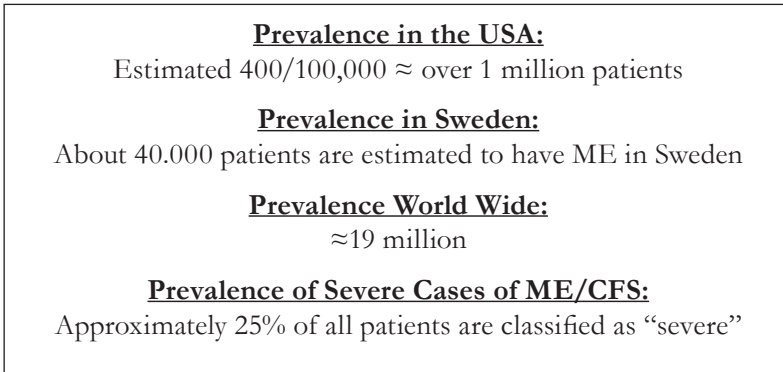


Figure 1. ME/CFS Prevalence and Severity World-wide.

Health (NIH) in the United States to prioritize the study of ME/CFS are encouraging. Without a significant increase in funding for these efforts, however, it is unlikely that either the intramural or extramural programs will make rapid or substantial progress in this difficult field.

There is a certain recognition of ME/CFS in Sweden, its effect on the citizenry and cost to society. This has resulted in excellent research targeted at immunological and pathological determinants of ME/CFS. However, access to care at the primary care level remains problematic. The relatively newly established clinic in Stockholm is an excellent start to remedy this problem. It would appear prudent for researchers and clinicians world-wide to collaborate in a networking fashion. This would ultimately allow for targeted research in countries and institutions with special expertise in the various aspects of the disease, as well as reaching consensus on appropriate diagnostic criteria, subsetting of patient groups, determination of endpoints for study, and appropriate therapeutic strategies. As in all other

chronic diseases, the driving force for these efforts must come from the patient groups and advocates in order to raise awareness in the appropriate government and private agencies to obtain the priority status and funding necessary to solve ME/CFS.

Sweden is unique in having a very well organized and functional national patient support organization, with local groups in the larger cities of Stockholm, Goteborg and Malmo. This patient organization is active in lobbying the government for necessary infrastructure, reform and funding.

Jonas Bergquist, PhD, at Uppsala University has been very instrumental in spearheading basic research into the biochemical metabolomics and proteomics in the serum and spinal fluid of patients severely affected by ME/CFS. The Gottfries Clinic in Molndal, Sweden, continues with its efforts to meet the demands of patients for diagnosis and treatment of fibromyalgia as well as ME/CFS. Jonas Blomberg, MD, PhD, a retired professor of clinical virology, remains active in his study of the role of viruses and immunity in the development



Figure 2. Economic Impact of ME/CFS. Annual Economic Loss Due to ME/CFS

of ME/CFS. Dr. Per Julin continues to develop and expand the ME/CFS clinic in Stora Skondal. Other physicians and centers are striving to develop appropriate institutions or clinics to serve the approximately 40,000 patients with ME/CFS in Sweden.

Most of the world's medical schools and medical textbooks do not include ME/CFS in their curriculum or publications, other than perhaps brief summaries and suggestions for symptomatic therapy.

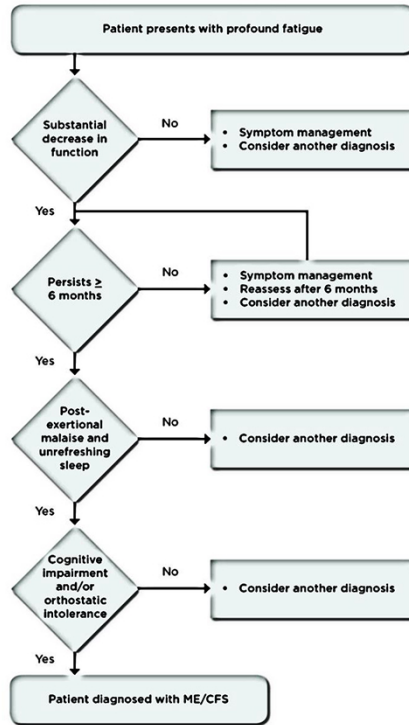
While education of primary care physicians and other practitioners is critical to the field, Centers of Excellence appear to be the most cost effective and viable approach to expediting translational medicine (the process of bringing bench research to the efficient diagnosis and treatment of patients). Worldwide collaboration, as exists in many other diseases such as multiple sclerosis, AIDS, and diabetes, would be ideal. It is difficult to establish the necessary infrastructures, particularly in view of differing funding mechanisms and distribution systems for medical care in dif-

ferent countries and diverse cultures. A Nordic coalition, however, might be plausible and should be explored. The National Center for Neuroimmunology and Emerging Diseases at Griffith University in Australia has been highly successful in developing the translational medicine concept, conducting state of the art basic and clinical research while simultaneously engaging in clinical diagnostic and treatment endeavors.

Name Change Controversy

In spite of the extensive publicity and discussion of the Institute of Medicine's (IOM) recommendations to establish new criteria for ME/CFS, there has not been broad support for adopting or endorsing SEID. While the clinical definition is very user friendly (it can be applied quickly by inexperienced clinicians), it is the general feeling that it does not capture a homogenous population. Leonard Jason, psychologist and researcher, has indicated that the SEID definition captured most of classically defined ME/CFS patients but included

Diagnostic Algorithm for ME/CFS



For more information, visit www.iom.edu/ME/CFS



Figure 3. SEID Diagnostic Algorithm for ME/CFS

a larger and less specifically uniform patient cohort.

Without acceptance by agencies such as the CDC, NIH, or WHO the definition may not be widely adopted. Additionally, in light of ongoing research initiatives, basic as well as clinical researchers have continued to use the long established and accepted definitions including the Canadian Consensus Criteria (CCC) and/or the 1994 CDC Criteria. Certainly there will continue to be re-evaluation and

discussions of the appropriate use of these established and newly proposed definitions due to the heterogeneous nature of the patient populations. Consensus, of course, is the ultimate goal.

Research Developments

Subsetting ME/CFS Patients

The heterogeneous nature of the populations obtained by the various definitions suggest that researchers and

clinicians must continue efforts at categorizing patients into subsets in order to determine the etiology and pathogenesis and, ultimately, the most appropriate treatment. Examples include the ongoing clinical trials in Norway and the UK with rituximab in patients presumed to have an autoimmune component to their pathogenesis. An example of translational medicine can be found in the work of professor Carmen Scheibenbogen of Berlin, Germany, describing auto-antibodies to adrenergic and acetylcholine receptors in ME/CFS patients which has both diagnostic and therapeutic implications for the patients. This may aid in understanding the autoimmune pathophysiology in a subset of patients. Such stimulating and exciting initial results, mandate additional and replicating studies.

After more than 30 years of studying ME/CFS worldwide, the preponderance of evidence continues to suggest a role of immune perturbation/dysfunction in the production of the signs and symptoms of the disease. As molecular biology has become fine tuned, researchers are capable of studying the nuances of B, T and Natural Killer Cell function. Many of the reported abnormalities such as impaired Natural Killer Cell function have been reproduced in independent laboratories. However, there is yet to be universal agreement as to the sensitivity and specificity of biomarkers for diagnosis or treatment.

Big Data and Precision Medicine

ME/CFS is a Big Data gold mine. Big Data has become in vogue as an

approach utilizing statistical methodology and modeling to study ME/CFS and many other clinical illnesses. While this approach is clearly of great potential, particularly with respect to precision medicine, it requires large numbers of patients and is a very costly approach to diagnosis. On the other hand, there remains a concern as to whether findings obtained in a small group of patients, such as the proposed NIH intramural study of 40 patients and controls, or the Stanford Initiative with 20 severely affected patients, will be applicable to the greater ME/CFS patient population. Worldwide, patients, clinicians, and researchers are anxiously awaiting the results of these preliminary studies utilizing the Big Data technology approach to the study of ME/CFS.

Precision medicine is yet another trend in medical research. Some success has been obtained, for example, in identifying the correct chemotherapeutic agent for treatment of various cancers, eliminating the inaccuracy and potential complications of trial and error therapy even when utilizing evidence-based studies. The NIH recently awarded \$55M for fiscal year 2016 to launch the Precision Medicine Initiative (PMI). This is a landmark research effort that aims to engage one million participants to prevent and treat disease based on lifestyle, environment and genetics. Perhaps ME/CFS patients will ultimately benefit from this effort. It remains to be determined whether these approaches utilizing genetic profiles, gene expression studies, metabolomics, etc., will have general applicability to the

diagnosis and treatment of patients with ME/CFS. Precision medicine is certainly a lofty goal with the potential for increased sensitivity and specificity of diagnosis and cost effective therapies.

The Gut Microbiome and ME/CFS

There is increasing evidence that the human microbiome is influenced by many factors and the status of the gut microbiome has significant impact on immunological function. This is an extremely complex area of study. The pursuit has been taken up by numerous well-respected research institutions including Columbia and Cornell Universities in New York. The potential utility for understanding the pathogenesis of ME/CFS or for determining strategies for treatment, remains to be determined. Hopefully, adequate funding for further large studies will be forthcoming.

Treatment of ME/CFS

Treatment of ME/CFS remains challenging and problematic. Since the publication of the P2P and IOM documents, there is agreement that additional work must be done in determining outcome measures for clinical trials. In addition, determination of appropriate interventions for clinical trials and execution at multiple sites with well-characterized subsets of patient populations are needed. Unfortunately, there has been little interest from the pharmaceutical industry which, in general, is the driving force behind well-constructed and funded clinical trials. It is hoped that agencies such as the FDA and others might be

engaged in the effort to design appropriate clinical trials and even support their execution. In the interim, clinicians on the front line of patient care must utilize the art of medicine in selecting modalities of intervention that have been demonstrated to potentially affect quality of life or prevent the devastating complications and comorbidities of chronic disabling illness. Large well-funded studies are required for international collaboration, particularly when studying genetics and gene expression of complex yet relatively frequent diseases such as ME/CFS. These should be conducted in well designed and executed studies at multiple sites utilizing only well characterized patients.

Obstacles and Solutions

As the P2P and IOM documents clearly point out, ME/CFS research has been fragmented and fraught with methodological pitfalls such as use of different disease definitions, lack of objective endpoints, small patient numbers, lack of control groups, failure to replicate results and numerous other shortcomings. The studies have largely lacked the scientific rigor sufficient for the world of evidence based diagnosis and management. Some of these stumbling blocks have been overcome by general acceptance of case definitions, emphasis on subsets and rigorous study designs. Yet, many obstacles remain for the nascent researchers and clinicians in this difficult and complex illness.

The largest of these obstacles is the failure of the scientific world (and in

some cases the patient community) to accept the existence of ME/CFS as a real, organically based disease, and associated with extreme disability. Fledgling efforts have been further hampered by profound lack of funding of the magnitude necessary to conduct even the basic rigorous studies and treatment interventions. Government agencies, academic institutions and the pharmaceutical industry have ignored the call to action, leaving funding to small grants and private donations.

It may be useful to remind ourselves of the magnitude of ME/CFS in the world in human and economic terms. Clearly such large numbers should justify the resources necessary to intensely study the disease and alleviate the concomitant disability and economic cost to all societies.

Using basic patient's samples such as blood, urine, saliva and CSF sophisticated research can be done on DNA, RNA, epigenetic markers, proteins, metabolites and immune cells and their messenger cytokines and chemokines.

New technology such as high output sequencing, big data mining, etc. will provide the necessary tools to solve these problems, but adequate funding must be obtained. It has been guesstimated that with adequate funding such as that allocated to other comparable old and emerging disease (e.g. Zika virus related disorders) ME/CFS could be fully understood and treated in 3-5 years. While it is unlikely that a single country or agency will step up to the financial plate, worldwide collaboration could accomplish

these goals.

In just the last few months the NIH has funded projects aimed at training patients to recognize exhaustion (precision medicine) and a broadly based large study to determine biomarkers (big data analysis and high tech molecular biological techniques).

Longitudinal studies to determine the natural history of ME/CFS are being conducted by the CDC at multiple sites using common data elements, standardized testing and data analysis. The International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) is again hosting their biannual meeting at the Weston Fort Lauderdale, October 27-30. Participation by researchers and clinicians, and patients are of course welcomed and encouraged.

One of the most unique and ubiquitous symptoms of ME/CFS is post-exertional fatigue following physical or cognitive challenge. Many centers are now studying this symptom to determine its cause, to seek a potential unique (sensitive and specific) biomarker and determine potential therapeutic interventions for this very disabling symptom.

A few large, classically designed treatment studies are being conducted while compassionate, empiric treatment protocols remain the standard of care.

Recently major strides have been taken to achieve common goals in Europe. Phenomenal progress has been made over the past ten years in the UK through the effort of the Invest in ME UK Charity to stimulate research and patient and physician

education. As an example, the Invest in ME Research Charity has launched the foundation for a translational biomedical research Centre of Excellence. It also sponsored a state of the art scientific meeting, affording invited scientists and clinicians the opportunity to share research and strategies while providing education and hope to patients and treating clinicians. The recent IIMEC11 conference presented stimulating new studies on case definitions, sub setting patient groups, the human, viral and bacterial gut microbiome, potential genetic and metabolomic biomarkers, and second generation research on a wide variety of immune markers including NK cells, B cells and cytokines. With proper support and leverage these areas all present viable and promising potential for future clinical researchers and clinicians.

Representatives of 13 countries in Europe have joined the European ME Research Group (EMERG) for international collaboration. This represents a major step in the development of a necessary regional infrastructure to support new research initiatives. Such collaborative efforts will maximize research speed and efficiency.

Conclusion

Throughout the world, access to care remains problematic for patients with ME/CFS. There remains a lack of knowledge on the part of most physicians at both the primary care and specialty level with respect to ME/CFS in general and particularly in the area of diagnosis and appropriate treatment. Strategies implemented to date have had limited success in encouraging clinicians to specialize in the area of ME/CFS or to even make an appropriate diagnosis. Given the long duration of this gaping hole in the provision of medical care, many experts feel that the appropriate funding and establishment of Centers of Excellence may be the most viable approach for educating physicians and ancillary personnel. Alas, while there is widespread support amongst patient groups and clinicians, the funding and infrastructure is not endorsed or supported for this approach. And yet, never before have the tools been so efficient and available for the study of complex diseases and the future is optimistic if the obstacles aforementioned and the many others can be uniformly overcome.

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