CFS is no longer CFS, and it was never ME

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5 December 2008
Last updated: 8 January 2009

The Centres for Disease Control and Prevention in the USA has adopted a more including criterion for chronic fatigue syndrome which is important to be aware of when reading scientific papers. It is important to know that the new criteria is so much "loosened up" that it encompasses 2,5% of the general population instead of around 0,4% as with the earlier criteria. How to stratify and group patients in future research is proposed. The use of disjoint sets of patients is encouraged.

Abbreviations

CDC	Centres for Disease Control and Prevention, USA.
CFS	Chronic Fatigue Syndrome
et al.	et alii (Latin) = and others
ME	Myalgic Encephalomyelitis

ME research

The Centres for Disease Control and Prevention in the USA (CDC) has adopted the Reeves (et al.) empirical definition of CFS from 2005 [6], after having used the Fukuda definition since 1994 [5]. The Fukuda definition was already not good for research into Myalgic Encephalomyelitis (ME) because it did not have important ME symptoms as mandatory. It was e.g. possible to have patients with depression (without ME) fulfilling the Fukuda definition.

The CDC states that ME is not the same thing as chronic fatigue syndrome [3]. This is correct because "the father of ME", Melvin Ramsay from England, was never member of the group that created the first CFS criterion 1988 for CDC (Holmes et al.)[4]. Ramsays description of ME included muscle phenomena, circulatory impairment and cerebral dysfunction [1]. These things are not required for any of the CDC CFS definitions [4][5][6].

The last years very little biomedical research has been made on ME with a strict ME definition, but ME patients have hoped that the use of the Fukuda definition in research, if used with care, indeed collects sufficient ME patients to get statistical significant results. Nevertheless, one must be aware that it is possible to produce a study with patients fulfilling the Fukuda definition without anyone having ME. E.g. it is possible for some people with depression to fulfil the Fukuda definition.

In my experience, all patients with ME complain about cognitive problems, temperature regulatory problems and post exertional malaise exceeding 24 h. Most ME patients have sleep dysfunction and intolerances to pharmaceutical drugs. Their cognitive function worsens with upright posture. These symptoms are not required for any of the CDC CFS criteria [4][5][6].

The Canadian definition requires for example post exertional malaise exceeding 24 h and sleep dysfunction, but circulatory impairment is not a mandatory symptom, making it different from the Ramsay definition [1].

Biomedical research into ME at risk

The situation has changed to the worse for ME research since 2005 when Reeves and others from CDC created a so called empiric definition for CFS. The problem is that it collects a more vast group of patients. With the Fukuda criterion the estimated prevalence is 0,4%, but with the Reeves definition the prevalence is 2,5% [7]. The Fukuda criterion already defines a heterogeneous group of patients, and one would wish that a more strict criteria is used, but instead one expands the group further so the CFS-Fukuda patients are in minority, only representing 15% of the CFS-Reeves group. Leonard Jason has criticized the CFS-Reeves criterion [8][9].

Below is a list of research that already have been made with the new loose and fuzzy CFS-Reeves definition. The list has been compiled by Tom Kindlon. Many people are not aware the fact that these articles are based upon a different definition, because many of the articles have obscured what kind of criteria that has been used. Science should be transparent and clear, but unfortunately articles have been accepted despite it requires quite some work in order to figure out which criteria that was used.

Since the CFS-Reeves definition started to be used, it is quite a mess. It is work demanding to sort out which article has used which definition, and what definition that have been used in the articles that the article refers to. Ultimately this puts the validity of the research at risk.

If things would work properly in the scientific world, CFS-Reeves should have been called something else than CFS, because it is a supergroup to something that is already defined. It is like calling all mammals for apes. Only because apes are a subgroup of mammals, it does not mean that all mammals are apes.

Suggestions for future research

Many ME patients around the globe are waiting for research that will lead to meaningful results, an understanding of the pathophysiology and pathogenesis, and ultimately a cure. The research is based on the very important decision of how to group the patients, therefore this shall not be performed with heedlessness.

The expansion of the CFS concept is a severe disappointment for patients with ME that are hoping that biomedical research will progress. Scientists are urged not to use the CFS-Reeves definition, instead using the limited resources in order to advance ME research.

It would be an advantage if it would be possible to use exclusive sets of patients (disjoint sets). For the already heterogeneous CFS-Fukuda set, it would be a benefit if one could exclude the ME-Ramsay (or ME/CFS-Canada) patients from the group, thus making it less heterogeneous. The excluded ME patients shall then form a separate group. In order to keep comparability to previous research, one should indeed also have a group based on the original CFS-Fukuda definition, during a time period of around 10 years.

Scientists are suggested to group patients as follows in the future:

1) Patients fulfilling ME-Ramsay [1], ME-Hyde [10] or ME/CFS-Canada [2].*
2) Patients fulfilling CFS-Fukuda [5] and do not fit into group 1.
3) Patients from both group 1 and 2 above, i.e. patients fulfilling CFS-Fukuda.

* Note: One of the three definitions proposed in group 1 above should be agreed upon using. The meaning is not to use all three simultaneously.

This solution would be helpful to the patients that have ME, but also to the patients that do not have ME but still CFS. A win-win situation for both group of patients, because it will most likely speed up biomedical research.

The severity of ME can vary greatly, therefore it is strongly recommended that data is stratified upon severity.

References

[1] A. Melvin Ramsay. Myalgic Encephalomyelitis and Postviral Fatigue States: The Sage of Royal Free disease. 2nd edition, Gower Medical Publishing, London 1988.

[2] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Bruce M. Carruthers, et alii. 2005, ISBN 0-7890-227-9, Haworth Medical Press Inc.

[3] CDC citation: "The name myalgic encephalomyelitis (ME) was coined in the 1950s to clarify well-documented outbreaks of disease; however, ME is accompanied by neurologic and muscular signs and has a case definition distinct from that of CFS." http://www.cdc.gov/cfs/cme/wb3151/chapter1/overview.html

[4] Chronic Fatigue Syndrome: A Working Case Definition. Holmes et alii. Ann Intern Med. 1988; 108:387-389.

[5] CDC Fukuda 1994 CFS Case Definition http://www.cdc.gov/cfs/cme/wb1032/chapter2/case-definition.html

[6] Reeves WC, et alii. Chronic fatigue syndrome--a clinically empirical approach to its definition and study. BMC Med. 2005 Dec 15;3:19.

[7] Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. William C Reeves, et alii. Population Health Metrics 2007, 5:5. http://www.pophealthmetrics.com/content/5/1/5

[8] Leonard A. Jason, Judith A. Richman. How Science Can Stigmatize: The Case of Chronic Fatigue

Syndrome. Journal of Chronic Fatigue Syndrome, Vol. 14(4), 2007.

[9] Problems with the New CDC CFS Prevalence Estimate. Leonard Jason, Ph.D., DePaul University, Co-Cure 10 Jun 2007 http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0706B&L=CO-CURE&P=R1422&I=-3&m=17418

[10] Definition of ME by Byron Marshall Hyde, Nightingale Research Foundation, Canada. http://www.nightingale.ca

List of articles based upon the CDC Reeves 2005 CFS criteria

Source Tom Kindlon (http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0706D&L=CO-CURE&P=R1718&I=-3).

1. Chronic Fatigue Syndrome -- A clinically empirical approach to its definition and study. William C. Reeves et alii. BMC Medicine Vol 3, 19. December 15, 2005. http://www.biomedcentral.com/content/pdf/1741-7015-3-19.pdf
2. Cognitive Dysfunction Relates to Subjective Report of Mental Fatigue in Patients with Chronic Fatigue Syndrome. Lucile Capuron, et alii. Neuropsychopharmacology. 2006 Aug;31(8):1777-84.
3. Coping styles in people with chronic fatigue syndrome identified from the general population of Wichita, KS. Nater UM, et alii. J Psychosom Res. 2006 Jun;60(6):567-573.
4. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. Rajeevan MS, et alii. Genes Brain Behav. 2006 Jun 1.
5. Early Adverse Experience and Risk for Chronic Fatigue Syndrome: Results From a Population-Based Study. Christine Heim, et alii. Arch Gen Psychiatry. 2006;63:1258-1266.
6. Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: results from a population-based study. William C Reeves, et alii. BMC Neurol. 2006 Nov 16;6:41. http://www.biomedcentral.com/content/pdf/1471-2377-6-41.pdf
7. The challenge of integrating disparate high-content data: epidemiological, clinical and laboratory data collected during an in-hospital study of chronic fatigue syndrome. Vernon SD, Reeves WC. Pharmacogenomics. 2006 Apr;7(3):345-54. http://www.futuremedicine.com/toc/pgs/7/3 Abstract:http://www.ncbi.nlm.nih.gov/sites/entrez/16610945 *The paper above was used to define CFS for the gene expression studies published in Pharmacogenomics. These Pharmacogenomics papers are the papers presented below.*
8. The postgenomic era and complex disease. J A Witkowski. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 341-343.
9. An empirical delineation of the heterogeneity of chronic unexplained fatigue in women. Uté Vollmer-Conna, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 355-364.
10. The validity of an empirical delineation of heterogeneity in chronic unexplained fatigue. Eric Aslakson, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 365-373.
11. Gene expression profile of empirically delineated classes of unexplained chronic fatigue. Liran Carmel, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 375-386.
12. Polymorphisms in genes regulating the HPA axis associated with empirically delineated classes of unexplained chronic fatigue. Alicia K Smith, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 387-394.
13. Gene expression correlates of unexplained fatigue. Toni Whistler, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 395-405.
14. Identifying illness parameters in fatiguing syndromes using classical projection methods. Gordon Broderick, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 407-419.
15. Exploration of statistical dependence between illness parameters using the entropy correlation coefficient. R Cameron Craddock, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 421-428.
16. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. Hong Fang, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 429-440.
17. Exploration of the gene expression correlates of chronic unexplained fatigue using factor analysis. Jennifer Fostel, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 441-454.
18. Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome. Brian M Gurbaxani, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 455-465.
19. Chronic fatigue syndrome and high allostatic load. Elizabeth M Maloney, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 467-473.
20. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. Benjamin N Goertzel, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 475-483.
21. Allostatic load is associated with symptoms in chronic fatigue syndrome patients. Benjamin N Goertzel, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 485-494.
22. Improved prediction of treatment response using microarrays and existing biological knowledge. Simon M Lin, et alii. Pharmacogenomics, Apr 2006, Vol. 7, No. 3, Pages 495-501.