Endoplasmic reticulum stress in Fabry, ME/CFS and long COVID

In our last video, Fabrienne explored protein misfolding and endoplasmic reticulum stress as a cause of Fabry disease. As a reminder, Fabry disease results from genetic mutations that affect a gene for a specific protein. This protein, an enzyme called α-galactosidase A, is necessary for the breakdown of a specific fatty substance called Gb3 or GL-3. When this enzyme doesn't work, this fatty substance accumulates in a cell organelle called lysosome. However, many Fabry mutations do not cause a complete loss of function of this enzyme, but still allow for the production of deficient enzymes. These mutations often belong to a mutation type called missense mutation, as explained in an earlier video. The production of these deficient enzymes, however, comes at a cost: it may cause a disruption of the protein production organelle of a cell, the endoplasmic reticulum. This affects a large part of a cell's protein production, not just the enzyme in question. This endoplasmic reticulum stress, abbreviated ER stress, is a secondary cause of Fabry disease, that is independent from lysosomal storage of Gb3.

Fabrienne's genetic variant does not cause lysosomal storage, but only ER stress. Other patients with her variant who received chaperone therapy, which aims at restoring correct protein production, and thus is proven to reduce ER stress, have reported that this approach is very effective. Therefore, it only makes sense that Fabrienne's symptoms stem from ER stress, not from Gb3 accumulation. Some of those symptoms are: exhaustion, neuropathic pain, gastrointestinal problems, vertigo, tinnitus. Fabrienne has long noted that there is an overlap between her non-specific Fabry symptoms and other disorders like ME/CFS and long COVID.[1,2,3] In this, she is not alone. So in this video, we are going to explore if ER stress might also explain some of the characteristics of these disorders. Of course, we cannot do experimental research, so we'll have to rely on literature research. So in this video, we will try to answer to question if ER stress can explain the similar problems that occur in non-classical Fabry disease, ME/CFS and long COVID. Of course, much has been written about the term ME/CFS and its shortcomings. The CFS part is without doubt problematic[4], but ME isn't a perfect description either. For now, we'll stick with the name ME/CFS, but please regard this video as a contribution to finding an appropriate name for this condition.

Can long COVID and ME/CFS be lumped together? There is research showing that these two entities represent two examples of a broader illness.[3] Additionally, the association between ME/CFS and virus outbreaks is not new. There have historically been reports of outbreaks of ME/CFS associated with virus epidemics. However, it has been difficult to link these outbreaks to specific viruses, with associations with polio, Epstein-Barr virus, influenza and Ross River virus having been reported.[4] One explanation is ruling out some of these associations; for example, norwegian researchers established a twofold increase in ME/CFS risk during an influenza epidemic, without actually verifying that all the affected patients really had influenza.[4] But it is likely that people with influenza-like symptoms during an influenza epidemic have in fact influenza. So is there a way to reconcile these findings?

First, what do viruses do? A virus is incomplete life; it's genetic material wrapped in a small packet of proteins. A virus has no ability to reproduce by itself, it needs to hijack a cell and trick it into copying the virus's genetic material and producing the proteins needed to form

new virus particles.[5] As such, viruses are known to cause ER stress, and in consequence, viruses have developed different ways of interacting with ER stress. Many viruses are known to cause ER-stress, including Epstein-Barr virus, several different coronaviruses and alphaviruses, to which Ross River virus belongs.[5] It has been demonstrated for a member of the picornavirus family, to which polio belongs.[5] The Epstein-Barr virus is particularly interesting. It is a very common virus, but many people, especially children, do not develop severe symptoms. Still, the virus often persists in the body, in a latent state.[4] Now, ER stress can trigger a transition of EBV from a latent to an active state.[5] So maybe, EBV infections don't simply cause ME/CFS, but people with a predispostion for ME/CFS may have a higher risk of symptomatic EBV infections to begin with.

And what about Q fever? Q fever is also associated with a post-acute infection syndrome that is similar to ME/CFS, however, Q fever is caused by bacteria called Coxiella burnetii. How does that fit? Well, Q fever, too, has been demostrated to cause ER stress.[6] There are more bacteria that are known to cause ER stress[7], and as a little test of the predictive value of our theory, we took a closer look, starting with Legionella pneumophila, which causes Legionnaires' disease. And indeed, this disease, too, is associated with long-term fatigue.[8] Another example: Brucella bacteria, too, may cause chronic brucellosis.[9] These three types of bacteria have one thing in common: they are intracellular bacteria, directly interfering with the metabolism of the cells they reside in. As is the case with Epstein-Barr virus, some of these bacteria may remain in the patient's body for prolonged periods of time.

Recurrent infections with these kinds of pathogens may occur, and persistent enterovirus infections have been suggested as a cause for ME/CFS[4], but this does not explain why some people recover quickly, others slowly, and some never. Now, let's consider what we discussed in our last video about ER stress in Fabry disease: different missense mutations can cause different levels of ER stress.[10] It might well be that some missense mutations cause a level of ER stress that is by itself problematic, and other mutations are harmless on their own, but together with other mutations, can cause a cumulative effect. That raises two questions: what is the cutoff value where ER stress becomes problematic, and what causes the worsening of symptoms over time. From what we know about Fabry patients, we would like to suggest the accumulation of misfolded proteins as an answer to both questions. ER stress becomes problematic when protein accumulation exceeds degradation, and this accumulation of proteins is what causes a worsening over time. We have no data to back this up, it's just inductive reasoning. This accumulation may occur slower or faster, depending on the number and severity of missense mutations in a patient. The rate of recovery from viral infections may then be described as a factor of the baseline of ER stress caused by a patient's missense mutations and the severity of the viral infection.

In this way, ER stress bridges the gap to genetic risk factors. Viruses and bacteria don't run in families, ME/CFS does, even though the exact genetic causes remain elusive.[11] Not even a predictable inheritance pattern can be established.[11] In some families, missense mutations may be more common than in other families, but the severity and number of these missense mutations can differ between family members in countless different combinations. Some of these variants might be associated with monogenic diseases, but the detrimental effects of these variants may not be severe enough to cause symptoms that allow for a clear diagnosis of this monogenic disease, and so they remain undetected.

Please note that different mutations may affect different types of tissue, and virus infections do the same. In this way, cumulative effects of missense mutations in numerous different combinations, plus potential infections with different types of viruses and bacteria, might lead to phenotypes that are different in detail between any two patients.

Thus, the endoplasmatic reticulum is a physiological system that is relevant in viral infections, specific bacterial infections and in genetic disorders. ER stress can explain the unpredictable inheritance patterns that are observed in families, why no single gene can be associated with ME/CFS and why such different virus infections and even bacterial infections can all cause similar consequences. But is there a link between ER stress and other phenomena that are associated with ME/CFS?

One symptom that is often associated with ME/CFS is post exertional malaise, feeling excessively tired even after mild physical or mental exercise.[12] At least physical exercise is directly linked to an increase in protein output.[13] So if the endoplasmatic reticulum has difficulty keeping up with the normal protein demand, this difficulty will be even greater when protein demand increases during exercise. The accumulation of misfolded proteins appears to be associated with physical fatigue.[14] Another bit of data we found: ME/CFS patients showed higher levels of reactive oxygen species after exercise[14], something which demonstratably may be caused by ER stress.[15] It would be interesting to know if the overall decrease in protein production due to ER stress also decreases the overall ability to function. Another open question: Cells types that have a high requirement regarding protein production are muscle cells, nerve cells and glandular cells. These appear to be particularly affected by ME/CFS. So, how does a cell's metabolic rate affect its response to ER stress?

Inflammation is a part of ME/CFS[16], and the links between ER stress and inflammation are many. ER stress causes inflammation, and inflammation worsens ER stress. It is well established that ER stress triggers an inflammatory response.[17]

Sleep, too, is linked to ER stress. Protein folding is an error-prone process[18,19], so even in healthy people, misfolded proteins accumulate with extended periods of activity. One theory is that sleep is necessary for the degradation of such misfolded proteins.[20] It appears possible that sleep feels unrefreshing when protein misfolding exceeds protein degradation even during sleep because of missense mutations that cause ER stress. Poor sleep quality is a characteristic of neurodegenerative diseases that are associated with protein misfolding like Alzheimer's disease and Parkinson's disease[20], although the direction of causality remains unknown.

It is well-established that ME/CFS is more common among women than men.[21] Some data suggest that women have a higher baseline protein production than men.[22] Because women do not, on average, have more muscles than men, breakdown of proteins must also occur at a higher rate in women.[22] We couldn't find any data if this makes women more susceptible to protein misfolding and ER stress. ME/CFS is also associated with mitochondrial dysfunction[21], and this, too, may be caused by ER stress.[23] Protein folding usually becomes more difficult with age.[20] In this sense, long-term ER stress due to infectious diseases or missense mutations would represent an early partial aging process.

In summary, literature points towards chronic ER stress as a new disease entity. Such a chronic ER stress disorder may occur as part of a monogenic disease like Fabry disease, as a post-acute infection syndrome after a viral or specific bacterial infections or as a consequence of the cumulative effect of missense mutations that, when studied individually, may appear benign. Different combinations of missense mutations might lead to a wide spectrum of individual manifestations. Chronic ER stress may also play a role in disorders like hypermobile Ehlers-Danlos syndrome, fibromyalgia, dysautonomia, endometriosis and post-acute COVID-19 vaccination syndrome, and possibly even in diagnoses like autism spectrum, attention deficit disorder and somatic symptom disorder.

There are genetic factors that are associated with ME/CFS, but even a large scale screening with fifteen thousand patients failed to find a definite genetic cause.[24] That's not because the methods aren't good enough; genetic testing is sufficiently well developed. So the problem must be in the way we analyze the data. We are getting no further because we are looking for relationships between ME/CFS and single genes. This points towards a fundamental misunderstanding of the nature of mutations in genes associated with monogenic diseases: benign polymorphisms might matter, as is the case in cancer research. For the last ten years, the ACMG guideline for the interpretation of genetic mutations has done much to spread the notion that genetic variants that are not severe enough to cause a monogenic disease are therefore benign and can be disregarded.[25] But studying genetic variants in isolation is not representative of the situation in actual humans, where genetic variants interact with countless other variants in unforeseeable ways. In cancer research, it's well established that benign polymorphisms might have disastrous consequences when they appear in specific combinations.[26] The ACMG approach creates a blind spot for potential cumulative effects. Genetic research has only existed for a few decades; it's too early to designate variants as definitely benign. In Fabry research, the ACMG definition of „benign" is even actively misused to write off certain variants, hampering research in general and directly harming individual patients.

Whatever their nature, genetic factors have been firmly established as a part of ME/CFS. Of course, that is a frustrating conclusion, but unfortunately, ME/CFS and long covid are not conditions that can soon be resolved within the snap of a finger.

One thing that is certain after reviewing scientific literature is that both ME/CFS and long covid are very real physical problems. Don't let anyone tell you it's just in your head. As for the different causes of ME/CFS that have been proposed, they all point to a common physiological system, and that system is the endoplasmic reticulum.

How about treatment prospects? Fabrienne always tries to remain positive, and never to think anything bad about anyone without due cause. However, we suspect that at the moment the pharmaceutical industry and some of the other interested parties are not trying to figure out how to cure ME/CFS, but how to monetize it. Apart from that, there have been experiments in cell cultures and animal models with chaperones to restore proper protein folding. The viability of these approaches in humans is unproven. ER stress exists for a reason; it's part of the human immune response. Interfering may cause long-term adverse effects, in which case pros and cons would have to be weighed. We expect that chaperones that are specific for affected proteins are the best option, but in many cases, those might be far away.

Is there anything patients can do? There is no quick and simple ER stress test available at your family doctor. Fabrienne's theory cannot be verified without laboratory analysis. At the moment, our best option may be a statistical analysis of genetic variants and associated symptoms, with a special focus on supposedly benign variants. But all of this is something for the future, maybe even a future video, whenever we have new information. For this video, it's time to wrap things up. If you have any questions, feel free to write, and have a wonderful day.

References:

1. https://a143t.org/en/parallelen-von-fabry-und-me-cfs-zufall/ (Accessed June 1st 2026)
2. Lenders M, Brand E. Fabry Disease: The Current Treatment Landscape. Drugs. 2021 Apr;81(6):635-645. doi: 10.1007/s40265-021-01486-1
3. Komaroff AL, Lipkin WI. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. Front Med (Lausanne). 2023 Jun 2;10:1187163. doi: 10.3389/fmed.2023.1187163
4. Hanson MR. The viral origin of myalgic encephalomyelitis/chronic fatigue syndrome. PLoS Pathog. 2023 Aug 17;19(8):e1011523. doi: 10.1371/journal.ppat.1011523
5. Li S, Kong L, Yu X. The expanding roles of endoplasmic reticulum stress in virus replication and pathogenesis. Crit Rev Microbiol. 2015 Jun;41(2):150-64. doi: 10.3109/1040841X.2013.813899
6. Adhvaryu H, Huang L, Long CM, Voth DE. The intracellular agent of Q fever, Coxiella burnetii, alters human alveolar macrophage metabolism and mitochondrial physiology. mBio. 2025 Sep 10;16(9):e0143625. doi: 10.1128/mbio.01436-25
7. Friedrich A, Beare PA, Schulze-Luehrmann J, Cordsmeier A, Pazen T, Sonnewald S, Lührmann A. The Coxiella burnetii effector protein CaeB modulates endoplasmatic reticulum (ER) stress signalling and is required for efficient replication in Galleria mellonella. Cell Microbiol. 2021 Apr;23(4):e13305. doi: 10.1111/cmi.13305
8. Gamage SD, Ross N, Kralovic SM, Simbartl LA, Roselle GA, Berkelman RL, Chamberlain AT. Health after Legionnaires' disease: A description of hospitalizations up to 5 years after Legionella pneumonia. PLoS One. 2021 Jan 11;16(1):e0245262. doi: 10.1371/journal.pone.0245262
9. Qureshi KA, Parvez A, Fahmy NA, Abdel Hady BH, Kumar S, Ganguly A, Atiya A, Elhassan GO, Alfadly SO, Parkkila S, Aspatwar A. Brucellosis: epidemiology, pathogenesis, diagnosis and treatment-a comprehensive review. Ann Med. 2023;55(2):2295398. doi: 10.1080/07853890.2023.2295398
10. Živná M, Dostálová G, Barešová V, Mušálková D, Svojšová K, Meiseles D, Kinstlinger S, Kuchař L, Asfaw B, Poupětová H, Vlášková H, Kmochová T, Vyleťal P, Hartmannová H, Hodaňová K, Stránecký V, Steiner-Mrázová L, Hnízda A, Živný J, Radina M, Votruba M, Sovová J, Trešlová H, Stolnaja L, Reková P, Roblová L, Honsová E, Rychlík I, Dvela-Levitt M, Bleyer AJ, Linhart A, Sikora J, Kmoch S. Misprocessing of alpha -Galactosidase A, Endoplasmic Reticulum Stress, and the Unfolded Protein Response. J Am Soc Nephrol. 2025 Apr 1;36(4):628-644. doi: 10.1681/ASN.0000000535
11. Dibble JJ, McGrath SJ, Ponting CP. Genetic risk factors of ME/CFS: a critical review. Hum Mol Genet. 2020 Sep 30;29(R1):R117-R124. doi: 10.1093/hmg/ddaa169
12. Pheby DFH, Friedman KJ, Murovska M, Zalewski P. Turning a Corner in ME/CFS Research. Medicina (Kaunas). 2021 Sep 25;57(10):1012. doi: 10.3390/medicina57101012
13. Thyfault JP, Bergouignan A. Exercise and metabolic health: beyond skeletal muscle. Diabetologia. 2020 Aug;63(8):1464-1474. doi: 10.1007/s00125-020-05177-6
14. Che X, Ranjan A, Guo C, Zhang K, Goldsmith R, Levine S, Moneghetti KJ, Zhai Y, Ge L, Mishra N, Hornig M, Bateman L, Klimas NG, Montoya JG, Peterson DL, Klein SL, Fiehn O, Komaroff AL, Lipkin WI. Heightened innate immunity may trigger chronic inflammation, fatigue and post-exertional malaise in ME/CFS. NPJ Metab Health Dis. 2025 Sep 3;3(1):34. doi: 10.1038/s44324-025-00079-w

15. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell. 2010 Mar 19;140(6):900-17. doi: 10.1016/j.cell.2010.02.034
16. Deumer US, Varesi A, Floris V, Savioli G, Mantovani E, López-Carrasco P, Rosati GM, Prasad S, Ricevuti G. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): An Overview. J Clin Med. 2021 Oct 19;10(20):4786. doi: 10.3390/jcm10204786
17. Sanchez CL, Sims SG, Nowery JD, Meares GP. Endoplasmic reticulum stress differentially modulates the IL-6 family of cytokines in murine astrocytes and macrophages. Sci Rep. 2019 Oct 17;9(1):14931. doi: 10.1038/s41598-019-51481-6
18. Li H, Sun S. Protein Aggregation in the ER: Calm behind the Storm. Cells. 2021 Nov 28;10(12):3337. doi: 10.3390/cells10123337
19. Lenders M, Rudolph E, Brand E. Impact of ER stress and the unfolded protein response on Fabry disease. EBioMedicine. 2025 May;115:105733. doi: 10.1016/j.ebiom.2025.105733
20. Hafycz JM, Naidoo NN. Sleep, Aging, and Cellular Health: Aged-Related Changes in Sleep and Protein Homeostasis Converge in Neurodegenerative Diseases. Front Aging Neurosci. 2019 Jun 11;11:140. doi: 10.3389/fnagi.2019.00140
21. Cortes Rivera M, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review. Diagnostics (Basel). 2019 Aug 7;9(3):91. doi: 10.3390/diagnostics9030091
22. Henderson GC, Dhatariya K, Ford GC, Klaus KA, Basu R, Rizza RA, Jensen MD, Khosla S, O'Brien P, Nair KS. Higher muscle protein synthesis in women than men across the lifespan, and failure of androgen administration to amend age-related decrements. FASEB J. 2009 Feb;23(2):631-41. doi: 10.1096/fj.08-117200
23. Syed AM, Karius AK, Ma J, Wang PY, Hwang PM. Mitochondrial Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Physiology (Bethesda). 2025 Jul 1;40(4):0. doi: 10.1152/physiol.00056.2024
24. DecodeME collaboration. Initial findings from the DecodeME genome-wide association study of myalgic encephalomyelitis/chronic fatigue syndrome (preprint). 2025. Link.
25. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30
26. Martinez SL, Kolodner RD. Functional analysis of human mismatch repair gene mutations identifies weak alleles and polymorphisms capable of polygenic interactions. Proc Natl Acad Sci U S A. 2010 Mar 16;107(11):5070-5. doi: 10.1073/pnas.1000798107

27. Naviaux RK, Naviaux JC, Li K, Bright AT, Alaynick WA, Wang L, Baxter A, Nathan N, Anderson W, Gordon E. Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci U S A. 2016 Sep 13;113(37):E5472-80. doi: 10.1073/pnas.1607571113
28. Komaroff AL, Lipkin WI. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. Front Med (Lausanne). 2023 Jun 2;10:1187163. doi: 10.3389/fmed.2023.1187163
29. Mundorf AK, Semmler A, Heidecke H, Schott M, Steffen F, Bittner S, Lackner KJ, Schulze-Bosse K, Pawlitzki M, Meuth SG, Klawonn F, Ruhrländer J, Boege F. Clinical and Diagnostic Features of Post-Acute COVID-19 Vaccination Syndrome (PACVS). Vaccines (Basel). 2024 Jul 18;12(7):790. doi: 10.3390/vaccines12070790