ME FORENINGEN

Sundhedsudvalget

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Vedr. ME/CFS videnskabsafdækningen: Principielle fejl og mangler

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ME Foreningen ønsker hermed at udtrykke vores bekymring over den snart afsluttede vidensafdækning af ME/CFS, som sundhedsministeren igangsatte i 2024. Vi anerkender ministerens intention om at sikre en grundig og evidensbaseret afdækning, men vi må desværre konstatere, at processen hidtil ikke lever op til de forventninger, der med rette kan stilles til en så vigtig indsats.

Vores kommentarer beror på de to eksterne leverandørers (Defactum og Implement) præsentationer af deres foreløbige resultater hhv. d. 22.11.24 og 04.02.25 (vores skriftlige feedback til disse præsentationer ses i bilag 1 og 2). Rapporterne forventes offentliggjort af Sundhedsstyrelsen i begyndelsen af marts 2025.

1. Manglende inddragelse af ME-patienter og ME-eksperter

På samrådsmødet den 28. november 2023 understregede ministeren nødvendigheden af at inddrage ME Foreningen og ME-patienterne. Alligevel blev kun to ME-patienter interviewet af Implement (+ en repræsentant for ME foreningen). Kun én af de to af ME Foreningen foreslåede ME-eksperter blev interviewet, og vedkommende har siden sendt en kritisk vurdering af leverandørens foreløbige resultater, mens Defactum kun indledningsvist inddrog en repræsentant ifm. udarbejdelse af projektbeskrivelse. Desuden er væsentlig international viden ikke integreret i arbejdet til trods for, at ME Foreningen løbende har stået til rådighed med litteratur.

2. Ensidigt fokus og mangelfuld litteraturudvælgelse

Vidensafdækningen blev oprindeligt placeret i den afdeling i Sundhedsstyrelsen, der har ansvaret for funktionelle lidelser – en beslutning, vi fandt påfaldende, da vidensafdækningen ikke skulle omhandle funktionelle lidelser. Senere blev opgaven dog overdraget til afdelingen for evidensbaseret medicin, men det reviderede udbudsmateriale udelod det grundlæggende spørgsmål om, hvorvidt ME er en somatisk eller funktionel lidelse. Denne udeladelse har medført, at op mod 80 % af den biomedicinske litteratur om ME, som er afgørende for korrekt diagnostik og behandling, er ekskluderet i vidensafdækningen. De to eksterne leverandører har derfor formentlig ikke anvendt den specifikke, internationalt anerkendte diagnose ME/CFS, (G93.3), men har i stedet fokuseret på ”fatigue”, dvs. kronisk træthed eller udmattelse, som herhjemme kategoriseres som en funktionel lidelse under betegnelsen ”almen træthed” med en anden diagnosekode (DR688A9).

3. Metodiske mangler og brug af forældede studier

Det ser ikke ud til, at de eksterne leverandørers to rapporter vil belyse ME/CFS biomedicinske natur, herunder mulige årsager og risikofaktorer, da afklaringen af dette er udeladt i vidensafdækningen. Også sygdommens epidemiologi (forekomst) afhængig af diagnostiske kriterier og alvorsgrad er udeladt. Dermed bliver det heller ikke muligt at sammenligne diagnosticeringen og behandlingsindsatsen for ME/CFS i Danmark med vores nabolande, da sygdommen i disse lande kategoriseres med WHOs diagnosekode G93.3 og ikke som en funktionel lidelse.

Defactums resultater bygger i høj grad på systematiske reviews, der primært omfatter studier foretaget før 2011. Disse studier anvender forældede diagnosekriterier, der bl.a. ikke inkluderer PEM – et nøglesymptom for ME/CFS. Dette svækker resultaternes validitet. Derudover er der inddraget svage, ikke-blindede studier med subjektive endemål, hvilket yderligere underminerer evidensgrundlaget.

4. Begrænset internationalt perspektiv

Implement formåede ikke at inkludere Storbritannien i deres undersøgelse – det land, hvor afdækningen af ME-vidensgrundlaget via NICE-rapporten 2021 i dag sætter standarden for ME i andre lande. Desuden er vigtige internationale konsensusudtalelser og guidelines fra blandt andet USA, Belgien, Tyskland, Østrig og Schweiz ikke tilstrækkeligt inddraget. Denne manglende inddragelse forringer muligheden for, at Danmark kan sammenligne sin praksis med internationale standarder.

5. Mangel på gennemsigtighed

ME Foreningen har gentagne gange anmodet om mulighed for at gennemlæse og kommentere de endelige rapporter fra Defactum og Implement inden offentliggørelse. Disse anmodninger er blevet afvist, hvilket rejser væsentlige spørgsmål om processens transparens.

6. Konsekvenser for danske patienter

Med den nuværende tilgang risikerer danske ME/CFS-patienter at blive diagnosticeret og behandlet på et niveau, der ikke er i overensstemmelse med internationale standarder. Det kan betyde, at patienter i Danmark afskæres fra at få adgang til de nyeste behandlingsmuligheder. Vi kan på baggrund af de to eksterne leverandørers vidensafdækning konstatere, at den internationale WHO-diagnose (G93.3) for sygdommen, som resten af verden bruger, i praksis ikke anvendes i Danmark, mens Defactums fremlæggelse lige så klart viste, at de behandlinger, som anbefales til ME/CFS i Danmark (Cognitive behavioral therapy og Graded exercise therapy) ikke har nogle positive langtidseffekter, og da heller ikke anbefales internationalt som helbredende behandling for ME/CFS.

Afsluttende bemærkninger

På baggrund af ovenstående vurderer ME Foreningen, at vidensafdækningen ikke giver et retvisende billede af den nuværende viden om ME/CFS. Vi finder det særlig problematisk, at vidensafdækningen ikke udfordrer den danske tilgang til ME som en funktionel lidelse. Dette står i kontrast til internationale standarder og risikerer at fastholde danske patienter i en uholdbar og effektløs behandlingssituation.

Det er vores håb, at denne tilbagemelding vil blive taget i betragtning i det fremtidige arbejde på området, der bør omfatte etablering af en arbejdsgruppe med deltagelse af internationale ME-eksperter således at danske ME/CFS-patienter kan få adgang til diagnose og behandling på linje med patienter i andre lande. Til slut vil vi gerne henvise til vedhæftede diagnose- og behandlingsvejledning udarbejdet af ME-ekspert Jesper Mehlsen (se bilag 3, obs. ikke offentliggjort endnu).

ME Foreningen står naturligvis fortsat til rådighed for dialog og vidensdeling, der kan bidrage til en forbedret praksis fremover.

Med venlig hilsen

ME Foreningen samt medlemmer i ME foreningens Advisory Board (Bernard Jeune, Lektor emeritus, Epidemiologi, Biostatistik og biodemografi (EBB), Jesper Mehlsen, Klinisk fysiolog
Peter la Cour, prof. Sundhedspsykolog og Vibeke Vind, senior scientist, biokemiker).

Bilag 1

Opfølgning på 'Præsentation af foreløbige resultater fra vidensafdækningen af ME/CFS' afholdt i Sundhedsstyrelsen d. 22.11.24

På baggrund af mødet sender vi her en række bekymringspunkter, som også blev fremhævet ved mødet. Vi håber meget, at I vil tage disse med i det videre arbejde med vidensafdækningerne, så kvalitet og relevans sikres.

Vi er i særdeleshed bekymrede for de resultater, der blev præsenteret fra Implements afdækning af erfaringer i relevante lande med organisering af behandlingstilbud samt diagnosticering og behandling af ME/CFS. Afdækningen besvarer i sin nuværende form på ingen måde det grundspørgsmål, der blev stillet, ligesom den heller ikke forholder sig kritisk til metode eller inkluderer den viden, der er tilgængelig. Vi vil understrege, at den oprindelige opgave, der blev stillet af ministeren, var en afdækning af ME – ikke af Funktionelle lidelser (FL):

"Der er afsat 1,5 millioner kroner i 2024 til en afdækning af evidensgrundlaget for diagnosticering og behandling af lidelsen ME/CFS (Myalgisk Encephalomyelitis/Chronic Fatigue Syndrome). Vidensafdækningen bør inddrage international forskning samt erfaringer i relevante lande. I vidensafdækningen bør inddrages relevante aktører med faglig viden om ME/CFS."

Dette understreges af ministerens udtalelse på samråd d. 28.11.23 fra Sophie Løhde (Minuttal: 39.40): Samråd d. 28.11.23

"Funktionelle lidelser er ikke en del af den afdækning, som vi sætter i gang nu. Vi har afsat 1,5 mio. kr. til vidensafdækning med henblik på at få afdækket evidensgrundlaget for diagnosticering og behandling af ME og sørger dermed også for at få inddraget international forskning og erfaring fra andre lande – og at der også inddrages relevante aktører i forbindelse med vidensafdækningen. Dette vil ske under indkøb af en ekstern leverandør. Vidensafdækningen kommer til at være offentlig tilgængelig."

Selvom I i Implement søger neutrale beskrivelser, så bør I som vidensorganisation ikke fravælge hverken en kritisk beskrivelse og tilgang eller at gøre rede for mulige fremtidstendenser og fremtidsscenarier. Det skal dertil siges, at vi fra ME-foreningen løbende har understøttet med relevant litteratur og nyeste viden, fx fra de lande, der indgår i afdækningen. Vi fremsender gerne litteraturen igen. Hvis dette ikke nuanceres, kan vi som forening kun tage afstand fra rapportens metode og resultater – også offentligt.

Nedenfor følger en række yderligere punkter til hhv. Implements og Defactums præsentationer samt opsummerende bemærkninger til Sundhedsstyrelsen.

Til Implements afdækning:

- Afdækningen beskriver behandlingsforløb for en gruppe patienter, som givetvis ikke har ME, men FL, da man ikke har forholdt sig til konsensuskriterierne for ME. Hvis der faktisk findes patienter med ME i FL-gruppen, må de tilhøre den absolut lettest ramte del af ME-spektret, idet de ellers ikke vil kunne klare de krævende gruppeforløb og transporten til og fra. Der mangler generelt klarhed over, hvor mange ME-patienter der har en FL-diagnose eller er blevet diagnosticeret på FL-centre.

- Afdækningen må holde sig til beskrivelsen af forekomsten af WHO-diagnosekoden for ME og ikke for FL. Når det drejer sig om beskrivelsen af FL, som selvfølgelig må inddrages, da ME pt. ligger under disse, må det være for at afklare, hvilke af disse patienter der har ME. Hvis det ikke kan afklares, må det beskrives, hvorfor det ikke kan opregnes. Landspatientregistrets registrering af WHO-koden for ME må gennemgås (og gerne på hvilke afdelinger denne er registreret). Det bør undersøges, hvor mange af de 15.000-20.000 ME-patienter i Danmark (ifølge prævalens) der har ME-diagnosen, hvor de er i systemet, hvilke behandlinger de får, hvor mange der er syge og sengeliggende, og hvor mange der er børn under 16 år. Ligesom Implement bør beskrive Mehlsen-klinikkens ME-patientmateriale. Her findes oplysninger på ca. 1.200 patienter, der er diagnosticeret regelret efter konsensuskriterierne.
- Problematikken ift. de anvendte diagnosekoder kan yderligere udfoldes: Ifølge diagnosevejledningen for FL kan danske læger stille diagnosen DG933A, men på FL-centrene er ME diagnosen kun stillet fire gange, hvilket ligger meget langt fra prævalensen for ME (0,2-0,4%). Det er 100% udtrykkeligt angivet af WHO at de danske FL-diagnoser ikke kan bruges til samkodning med ME-diagnosen under multiple parenting[i]. I opgørelsen kan der derfor ikke pludselig argumenteres for, at to FL-diagnoser i virkeligheden er ME DG933A. Ingen ved hvad de dækker over. Kort sagt: Danske patienter fra FL-centre ved ikke, om de har ME, fordi FL-centrene ikke anvender opdaterede diagnosekriterier med PEM for DG933A – og der kan derfor ikke interviewes mere end fire patienter (i perioden frem til 10.05.2021) om ME i dette regi. Relevante patienter m.v. bør derfor findes i andet regi.
- Afdækningen bør inkludere og beskrive de sværest syge, herunder de permanent sengeliggende, bl.a. ved at søge oplysninger om ME-patienter, som har fået førtidspension, evt. også ved at inddrage avisartikler i BT, Se og Hør, lokale aviser m.fl. Disse er blandt andet også beskrevet her: https://www.tandfonline.com/doi/full/10.1080/27707571.2024.2359958.
- Afdækningen mangler (ud fra det vi fik præsenteret) status på curriculum om ME på medicin og speciallægeuddannelsen; status på medicinsk behandling af generelle symptomer og af ME specialiserede symptomer, og status på hvorvidt kurser i FL omfatter viden om ME med PEM.
- Afdækningen bør inddrage den danske del af den europæiske interviewundersøgelser af over 500 danske patienter https://www.europeanmealliance.org/documents/emeaeusurvey/EMEAMEsurveyreport2024.pdf https://me-foreningen.dk/wp-content/uploads/2024/11/Paneuropaeisk-danske-tal.pdf ligesom der også er værdifuld viden i ME-Foreningens medlemsundersøgelser fra 2008, 2014 og 2019 (vi stiller gerne data til rådighed, https://me-foreningen.dk/wp-content/uploads/2016/10/Sp%C3%B8rgeskemaunders%C3%B8gelse-2012-2.0-kopi.pdf, https://me-foreningen.dk/wp-content/uploads/2020/06/Medlemssurvey-2019-561-patienter.pdf). Der findes også tilsvarende i de omkringliggende lande, ikke mindst den selvstændige norske rapport af over 5000 norske ME-patienter.
- Afdækningen af Tysklands tilgang bør inddrage den konsensusvejledning om diagnostik og behandling af ME, som Tyskland har lavet i samarbejde med Østrig og Schweiz i maj 2024. Dette D-A-CH Konsensus statement er grundlaget for det videre arbejde med ME i Tyskland. https://link.springer.com/article/10.1007/s00508-024-02372-y
- Som tidligere rejst, så er det meget beklageligt, at Implement ikke har kunnet få fat i relevante kilder i UK. I den forbindelse blev en rapport fra 2023 om implementeringen af NICE2021 i UK tilsendt, som der som minimum bør refereres til, da den giver svar på det meste om ME i UK efter NICE2021.

- Endelig bør der også henvises til den nyligt publicerede embedslægerapport fra England om forebyggelse af dødsfald ved ME https://www.judiciary.uk/prevention-of-future-death-reports/maeve-boothby-oneill-prevention-of-future-deaths-report/. Det blev nævnt på mødet, at der i Danmark er oprettet to højt specialiserede funktioner til de sygeste patienter, men det er vigtigt at præcisere, at det er til patienter med funktionel lidelse uden specialiseret ME-behandling. Ligesom I England har Danmark ikke en eneste sengeplads eller anden sundhedsydelse til patienter med svær ME.

Til Defactums afdækning:

- For at være sikker på, at den inkluderede målgruppe er korrekt, bør søgningen begrænses til undersøgelser, der inddrager PEM.
- Det er i orden at fokusere på systematiske reviews og klinisk kontrollerede forsøg, men afdækningen må kritisk tage stilling til, hvad der ikke kan/bliver afklaret i disse typer studier. Fx de mange epidemiologiske undersøgelser, som har sammenlignet hyppigheden på samme stikprøver afhængigt af, hvilke diagnostiske kriterier man anvender. Dette bør inkluderes i en diskussion af metoden, som er meget væsentlig.

Til Sundhedsstyrelsen:

- Som det også blev fremhævet til mødet, vil vi meget gerne deltage i et opfølgende møde, hvor vi får mulighed for at se Defactums resultater. Hvis dette ikke er muligt, vil vi meget gerne have rapporten til kommentering. Det samme gælder for den færdige udgave af Implements rapport.
- Vi håber (set i lyset af de mange kommentarer til afdækningerne og generel god skik), at I vil sende begge rapporter i eksternt review blandt internationale ME-eksperter. Hvis det ikke er muligt at oversætte rapporterne, bør de som minimum sendes til nordiske eksperter. Vi vil meget gerne bidrage med forslag til specifikke personer.
- Desuden vil vi meget gerne høre mere om processen efter rapporterne er afleveret til jer. Nedsættes der fx en arbejdsgruppe med SST og eksterne ME-eksperter, der kan trække konklusioner og evt. anbefalinger til Sundhedsministeren fra de to rapporter? Eller hvad vil processen være? Dette stod ikke helt klart på mødet.
- Endelig vil vi gerne høre, hvad processen er for de to leverandører: Vil de udgive rapporterne?

[i] [i] "Multiple parenting" er en paralelldiagnosticering som WHO kun anbefaler til 2 diagnoser som supplerer hinanden. ME G93.3 og FL-diagnosen "almen træthed" udelukker gensidigt hinanden og derfor er "multiple parenting" ikke et begreb der kan anvendes her. Ifølge WHO må der ikke anvendes 2 koder for samme sygdom/symptomer: Fx udelukker ME G93.3 – ifølge WHO - diagnoser som MG22 træthed og Neurasteni F48.

Bilag 2

Opfølgning på mødet: Præsentation af foreløbige resultater fra vidensafdækningen af ME/CFS gennemført af Defactum d. 04.02.24

Tak for at holde et opfølgende møde, hvor vi fik præsenteret de foreløbige resultater og fik mulighed for at komme med vores input. Nedenfor følger en skriftlig tilbagemelding med en uddybning af de punkter, der blev fremhævet på mødet, som vi håber, I vil inkludere i det videre arbejde. Som tidligere fremført vil vi meget gerne gennemlæse rapporten og komme med skriftlige kommentarer hertil.

Basal viden om sygdommens karakter:

- **Der er en gennemgående og afgørende mangel på basal viden om sygdommen.** Hvis man ønsker en hurtig og umiddelbar introduktion, kan man fx spørge OpenAI, som opsummerer det meget fint. Se bilag 1 til dette dokument.

  OpenAI's rapport giver et solidt biokemisk og patofysiologisk grundlag for forståelsen af ME og PEM. Det kunne være relevant for Sundhedsstyrelsen at læse denne opsummering[1].

  Som immunologen Derya Unutmaz fra Jackson Laboratory udtrykker det: OpenAI's dybdegående forskningsrapporter er "ekstremt imponerende, troværdige og på niveau med eller bedre end publicerede review-artikler."[2]

Opgavens formål og resultater vedr. diagnose:

- **Opgaven gik ud på at belyse:** *"Hvilke kliniske undersøgelser, parakliniske og diagnostiske test og kriterier bør indgå ved mistanke om ME"*.

  Det blev bekræftet, at der ikke findes en simpel biomarkør til diagnosticering, hvilket også gør sig gældende for mange andre sygdomme, hvor diagnosen stilles på baggrund af kliniske symptomer, fx migræne.

- **Manglende inklusion/fokus på diagnosekriterier**: Det fremgik på mødet, at der i rapporten vil foreligge en række forskellige diagnosekriterier, der bør indgå ved mistanke om ME, men det fremgik ikke, hvad der vil blive oplyst om dem.

  Diagnosekriterierne for ME/CFS har udviklet sig meget de sidste 25 år, idet de er gået fra at være meget brede kriterier, der medtager træthed af mange typer og af mange årsager og har bevæget sig frem til langt mere specifikke og dermed snævre kriterier. De internationale konsensuskriterier (Carruthers et al 2011[3]) er formentlig det afgørende vendepunkt mellem de gamle og de nye forståelser. Det er her, at PEM bliver et nødvendigt, men ikke tilstrækkeligt hovedsymptom for

[1] https://www.nature.com/articles/d41586-025-00377-9;
[2] https://x.com/DeryaTR_/status/1886487553387430396
[3] Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus criteria. J Intern Med. 2011;270(4): 327-38. PMID: 21777306.

ME/CFS. Mayo-klinikkens diagnostiske procedurer for ME/CFS omtaler PEM som patognomonisk symptom, dvs. både nødvendigt og tilstrækkelig[4],[5].

Der er meget store forskelle på de prævalenser, men kommer frem til ved anvendelse af brede og specifikke kriterier. De anvendte diagnosekriterier er også af afgørende vigtighed for, hvilken gruppe patienter man undersøger i forhold til behandlinger.

Ved alle andre sygdomme uden biomarkør findes der også en række kliniske kriterier for sygdommen, fx for demens. Disse kriterier udvikler sig historisk og bliver i reglen mere og mere specifikke for sygdommen og adskiller den fra andre. Der opstår i tiden konsensus om, hvilke kriterier, der bør anvendes i forskningen om ME/CFS på nuværende tidspunkt, og kriterierne må angives specifikt, idet forskning med et sæt kriterier ikke kan sammenlignes direkte med forskning med andre kriterier.

Som det blev anført på mødet, viser de såkaldte "cykeltests", at der kan påvises klare biologiske forskelle i energiforvaltningen hos patienter defineret nutidsvarende med ME/CFS og immobile patienter, der lider af andre former for træthed, der kan indfanges af bredere definitioner. De anvendte kriterier er derfor af yderste vigtighed omkring en nutidig beskrivelse af ME/CFS.

Rapporten bør indeholde en redegørelse for og overblik over udviklingen af (og diskussion om) diagnosekriterierne for ME/CFS, hvilket er god videnskabelig praksis omkring kliniske symptomdiagnoser.

- **Internationale diagnosekriterier**: Der findes forskellige international anerkendte diagnostiske kriterier, som har udviklet sig over tid, hvor de nyeste alle indeholder symptomet PEM sammen med en gruppe af andre symptomer. Vores nabolande, der diagnosticerer G93.3 anvender ofte Canada-kriterierne. Da det er målbart, at patienter med PEM adskiller sig fra kontroller er det en vigtig parameter. Hvis man anvender kriterier uden PEM fx Oxford eller de danske kriterier for funktionelle lidelser, som ikke anvendes internationalt, risikerer man at diagnosticere en patient med ME uden patienten har den sygdom. Det bør fremgå af rapporten

Opgavens formål og resultater vedr. behandling:

- **Opgaven gik ud på at belyse:** *"Hvilken behandling farmakologisk og non-farmakologisk (herunder pacing), der bør anvendes til voksne med ME"*.

- **Graded exercise therapy (GET):** Dette afsnit hviler meget på Cochranes review, som i 2019 blev vurderet til at være forældet[6]. Der står således i reviewet: "All studies were conducted with outpatients diagnosed with 1994 criteria of the Centers for Disease Control and Prevention or the Oxford criteria, or both. Patients diagnosed using other criteria may experience different effects". Reviewet er derfor ikke gældende i sin nuværende form for ME defineret med nyere diagnose-

[4] Consensus recommendations (2021): Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management - Mayo Clinic Proceedings
[5] Consice review for clinicians (2023):Diagnosis and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
[6] Publication of Cochrane Review: 'Exercise therapy for chronic fatigue syndrome' | Cochrane

kriterier. Ydermere er reviewet kun gældende for ambulante patienter (outpatients) (mild ME), og ikke for moderat, severe og very severe ME, der udgør mere end halvdelen af patientgruppen.

Det fremgik af Defactums præsentation at "alvorlige bivirkninger er sjældne og ligeligt fordelt mellem grupperne", men der står i reviewet, at de er dårligt belyst "the evidence regarding adverse effects is uncertain". Da dem, der får det dårligt af træning, er dem, som har PEM, kan man ikke konkludere, at bivirkninger er sjældne. Dette bør tydeligt fremgå af rapporten.

- **Cognitive behavioral therapy (CBT):** I dette afsnit er der inkluderet et systematisk review, hvor der står: "Most studies (k = 10) used the international definition criteria (Centers for Disease Control and Prevention, [1]) for inclusion of CFS patients, while the other studies either used the Oxford criteria ([22], k = 3), or cut-off values (k = 2)". Sætningen fra Cochranes review om GET, må derfor også gælde her:" Patients diagnosed using other criteria may experience different effects". Ydermere er nogle af studierne kun gældende for mild/moderat ME. Dette bør tydeligt fremgå af rapporten.

Metodediskussion:

- **Manglende basal viden om sygdommens karakter – og betydning for udvælgelse af studier:** Vi fik fra præsentationen det indtryk, at det basale overblik over, hvilken sygdom man har med at gøre, ikke har været retningsgivende i udvælgelsen af hvilke artikler, man udvalgte at gå videre med i opgavens anden del.

- **Manglende viden om, hvilke kriterier, der var givet for inklusion i de udvalgte undersøgelser:** Det fremgik af en slide i præsentationen, at der er gennemgået 8 studier, og at de 7 af disse studier er foretaget før 2011, hvor konsensuskriterierne udkom – og det senere studie fra 2017 angiver, at anvende helt brede, nu ud-daterede kriterier for CFS (ME er overhovedet ikke nævnt i studiet). Der er altså anvendt kriterier, hvor PEM ikke er medtaget. Resultaterne fra disse studier kan derfor ikke overføres til ME/CFS patienter. Det vil være en metodefejl at overføre resultater fra en patientgruppe til en anden patientgruppe – og der må som minimum gøres ganske udtrykkeligt opmærksom på dette forhold, hvilket vi også forventer, at det gøres i den endelige rapport. Andet vil være videnskabeligt forkert.

- **Inklusion af svage studier:** Alle de enkelt-studier for GET og GBT, der indgår i de systematiske reviews er meget svage (tæt på ikke-valide), da det er ikke-blindet studier med subjektive endemål. PACE-studiet indgår i begge reviews, selvom det er fejlbehæftet. Det bør være den korrigerede genberegning, der anvendes[7]. Dette bør også tydeligt fremgå af rapporten.

- **Manglende inklusion af europæiske) guidelines/HTA-rapporter:** I inklusionskriterier for begge review står der, at (europæiske) guidelines/HTA rapporter fra større anerkendte institutioner ønskes inddraget. Ud fra præsentationen så det ikke ud til, at disse er blevet inddraget. Der findes

[7] Rethinking the treatment of chronic fatigue syndrome—a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT | BMC Psychology | Full Text

for eksempel en europæisk NICE-guideline[8] og en amerikansk IOM-rapport[9], der beskriver hvordan ME diagnosticeres og tilgås med hensyn til behandling og pleje. Her fremgår det meget tydeligt, at pacing ikke er en behandlingsform – det kan derfor ikke undersøges i RCT'er – men en måde at undgå at udløse PEM og få forværring. Det fremgår også, at simpel symptomlindring er vigtig for at bedre patienternes meget ringe livskvalitet. Dette tilbydes andre patientgrupper uden der skal foreligge RCT'er, så det bør også gælde for ME-patientgruppen. Dette bør tydeligt fremgå af rapporten.

- **General diskussion af metode**: Defactum bør som vidensorganisation ikke fravælge hverken en kritisk stillingtagen til formål, metode og resultater – ej heller ikke selvom resultaterne bygger på et systematisk review. Det er ikke tydeligt for os, hvordan det vil fremgå i rapporten.

Konsensusarbejde fra andre lande:

- **Opmærksomhed på den internationale konsensus på området:** Andre landes sundhedsmyndigheder har, uafhængig af hinanden, konkluderet at ME er en kronisk, multisystemisk sygdom: USA (2014), USA (2015), USA (2016), Nederlandene (2018), Belgien (2020), Storbritannien (2021), USA (2023) og Tyskland (2023). Tyskland/Østrig/Schweitz (2024) Dette bør som minimum indgå i baggrund eller diskussion.

[8] Evidence reviews - October 2021 | Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management | Guidance | NICE

[9] Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness - PubMed

Myalgic Encephalomyelitis (ME/CFS)

Pathobiology, diagnosis, and treatment

Jesper Mehlsen, MD

About the Author

Jesper Mehlsen is medical doctor graduated from the University of Copenhagen in 1979 and a specialist in Clinical Physiology. As such his primary clinical work and research has been focused on complex medical conditions – in particular those that involves dysfunction of the autonomic nervous system.

Jesper Mehlsen has worked clinically with patients suffering from myalgic encephalomyelitis for more than 10 years and has diagnosed and treated more than 2,000 patients with this disease. Jesper Mehlsen is the current chairman of the European ME Clinician's Council.

Jesper Mehlsen has mor than 300 publications - 175 in peer reviewed medical and technical journals. Jesper Mehlsen is co-chairing the European ME Research Group and is co-chairing the ME/CFS Clinical Trial Working Group under the National Institute of Health, USA.

Preface

The myalgic encephalomyelitis (ME) stems from Latin: myalgia i.e., pain in a muscle or groups of muscles and inflammation of the brain (encephalon) and the spinal cord (myelon). The diagnosis was first use to describe a multiorgan disease epidemic at the Royal Free Hospital in London in an editorial in the Lancet in 1956. An outbreak of a similar condition occurred in Nevada 1984 and was given the more generalized term Chronic Fatigue Syndrome (CFS) by the Centre for Disease Control in 1984 and hence the short form ME/CFS. The diagnosis of ME has been recognized by WHO since 1969 and is - in the current disease classification - listed under the group of Postviral and related fatigue syndromes with the specific code of G93.32.

ME/CFS is a disabling chronic inflammatory condition causing generalized symptoms affecting multiple organ systems and leading to invalidity ranging from partial incapacitation in daily activities to a severe condition in which the patient is bedridden, dependent on care 24/7 and sometimes needing tube feeding. In the severe stage, the patient is hypersensitive to light and sound, often unable to communicate in a normal fashion and has a very low stress level. Even though ME/CFS is a life-long condition it is possible with the right care and treatment to achieve a lower severity level over months to years.

Like in many diseases and illnesses, such as the common cold, migraine headaches, generalized pain and others, ME/CFS lacks a single and accurate biomarker. Many countries have developed guidelines for diagnosis, treatment, and care based on scientific evidence and achieved consensus. In 2011 an international group of clinicians and researchers working with ME/CFS published a consensus on a medical case definition for the diagnosis of ME/CFS. Quantitative support for the diagnosis and for grading of severity can be obtained through validated questionnaires as well as by testing physical and cognitive functions, and through laboratory analyses.

The contents of this expert report are based on clinical experience from more than 2,000 ME/CFS patients combined with intensive studies of the vast literature on pathobiology and suggested treatments in this group of patients.
Part 1 of the report is focused on diagnosis, probable causes, and background.
Part 2 of the report describes possible treatment options for mitochondrial dysfunction, neuroinflammation, and autonomic dysfunction.

Frederiksberg February 2025

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Section 1: Diagnosis, Probable Causes & Background

Section 2: Treatment

Section 1

1. 1. Screening diagnosis – Institute of Medicine Criteria for ME/CFS

The Institute of Medicine (IOM) has proposed simplified criteria for the diagnosis of ME/CFS. According to these criteria differential diagnoses should be excluded and the patients must have the following three symptoms and at least one of two other manifestations.

A. A substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that:
    a. lasts for more than 6 months,
    b. is accompanied by fatigue that is:
        i. often profound
        ii. of new onset (not life-long)
        iii. not the result of ongoing or unusual excessive exertion
        iv. not substantially alleviated by rest

B. Post-exertional malaise (PEM) - worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness. PEM often puts the patient in a relapse that may last days, weeks, or even longer. For some patients, sensory overload (light and sound) can induce PEM. The symptoms typically get worse 12 to 48 hours after the activity or exposure and can last for days or even weeks.

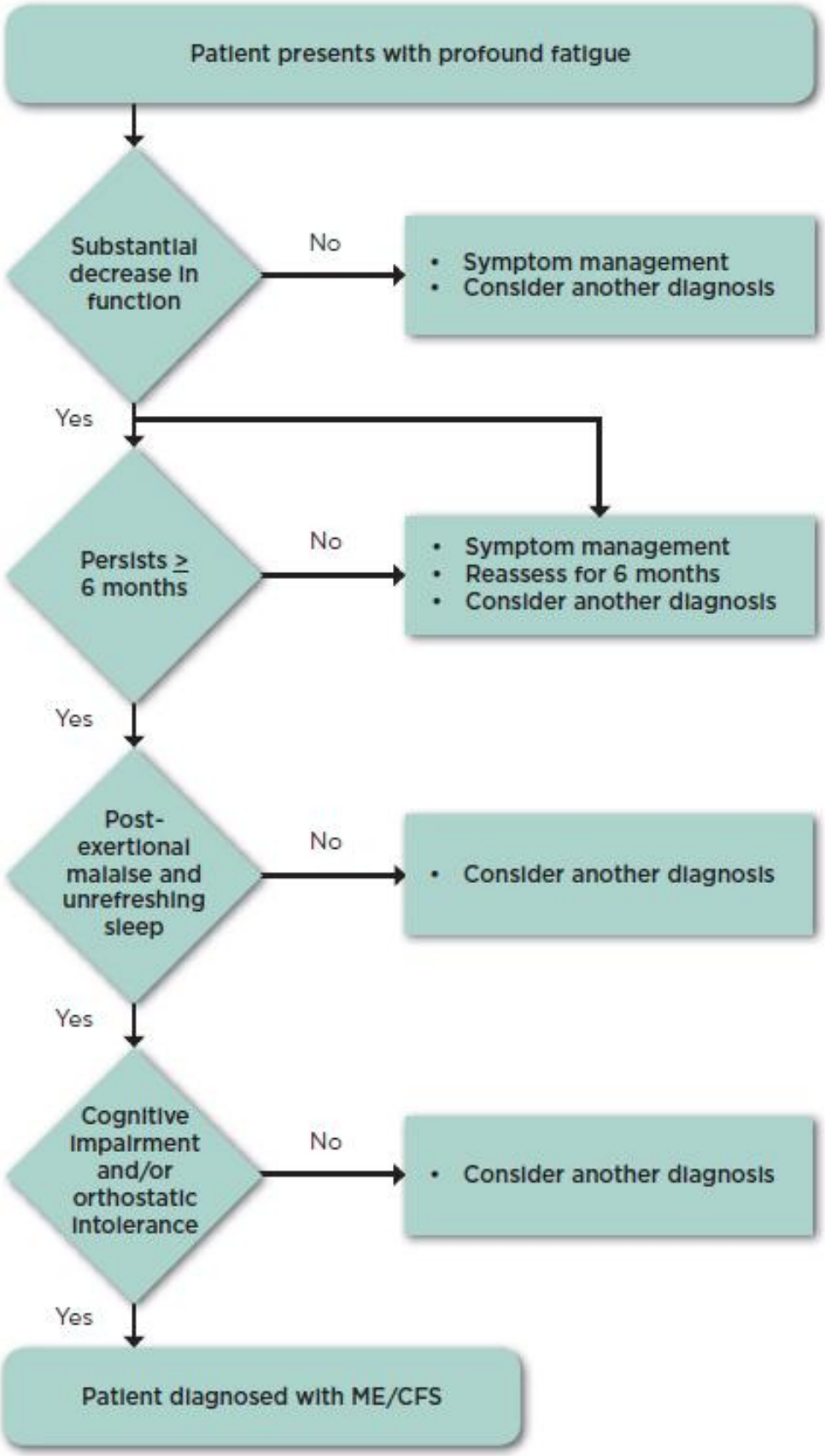
C. Unrefreshing sleep—patients with ME/CFS may not feel better or less tired even after a full night of sleep despite the absence of specific objective sleep alterations.

At least one of the following **two additional manifestations** must also be present:

1. Cognitive impairment—patients have problems with thinking, memory, executive function, and information processing, as well as attention deficit and impaired psychomotor functions. All can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure, and may have serious consequences on a patient's ability to maintain a job or attend school full time.

2. Orthostatic intolerance—patients develop a worsening of symptoms upon assuming and maintaining upright posture as measured by objective heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing. Orthostatic symptoms including lightheadedness, fainting, increased fatigue, cognitive worsening, headaches, or nausea are worsened with quiet upright posture (either standing or sitting) during day-to-day life and are improved (though not necessarily fully resolved) with lying down. Orthostatic intolerance is often the most bothersome manifestation of ME/CFS among adolescents.

1.1.1. Diagnostic algorithm for ME/CFS according to Institute of Medicine, USA



1.1.2 Final diagnosis for ME/CFS - International Consensus Criteria (ICC)

Differential diagnoses must have been excluded. Patients must – to receive the diagnosis of myalgic encephalomyelitis - meet the criteria for post exertional malaise, and have:

A. at least one symptom from three neurological dysfunctions
B. at least one symptom from three immunologic/gastrointestinal/genitourinary change categories
C. at least one symptom from energy metabolism/mobility impairments.

Post-exertional Malaise (PEM): Mandatory

A pathological inability to produce sufficient energy as needed with prominent symptoms in the neuroimmune areas.

Characteristics are as follows:

- Pronounced, rapid physical and/or cognitive fatigue in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, may be disabling and cause relapse.
- Worsening of symptoms after exertion: e.g., acute flu-like symptoms, pain and worsening of other symptoms.
- Post-exertional fatigue can occur immediately after activity or be delayed by hours or days.
- The refund period is extended and usually takes 24 hours or longer. A relapse can last days, weeks or longer.
- Low threshold for physical and mental fatigue (lack of endurance) results in a significant reduction in activity level before illness.

Notes: To be diagnosed with ME, symptom severity must result in a significant reduction in a patient's premorbid activity level.

- *Mild (approx. 50% reduction in activity level before illness),*
- *Moderate (mostly at home),*
- *Severe (mostly bedridden) or*
- *Very severe (completely bedridden and needs help with basic functions).*

There can be marked fluctuations in symptom severity and hierarchy from day to day or hour to hour. Consider activity, context, and interactive effects.
Regardless of a patient's recovery time after reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if possible.
Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities sufficiently.

Neurological disorders

At least one symptom from three of the following four symptom categories:

Cognitive dysfunction

- Difficulty processing information: slowed thinking, reduced concentration, e.g., confusion, disorientation, cognitive overload, difficulty making decisions, slowed speech, acquired or effortful dyslexia.
- Short-term memory loss: e.g., difficulty remembering what you wanted to say, what you said, retrieving words, recalling information, poor working memory.

Pain

- Headache: e.g., chronic, generalized headache often involves tenderness in the eyes, behind the eyes, or in the back of the head that may be associated with cervical muscle tension; migraine; tension headache.
- Significant pain can be experienced in muscles, muscle-tendon connections, joints, abdomen, or chest. It is non-inflammatory in nature and often migrates e.g., generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain.
- Disturbed sleep patterns: e.g., insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, waking much earlier than before onset of illness, vivid dreams/nightmares.
- Unrefreshing sleep: e.g., waking up feeling exhausted regardless of the duration of sleep, daytime sleepiness.
- Neurosensory, perceptual, and motor disturbances
- Neurosensory and perceptual: e.g., inability to focus vision, sensitivity to light, noise, vibration, smell, taste, and touch; reduced depth perception.
- Engine: e.g., muscle weakness, twitching, poor coordination, unsteadiness on the feet, ataxia.

Notes: Cognitive dysfunction - reported or observed - becomes more pronounced with fatigue. Overload phenomena can be evident when two tasks are performed simultaneously. Abnormal pupillary accommodative reactions are common.

Sleep disorders are typically manifested by prolonged sleep, sometimes extreme, in the acute phase and often develop into significant sleep changes in the chronic phase.

Motor disturbances may not be evident in mild or moderate cases, but abnormal gait and positive Romberg test may be observed in severe cases.

Immunological, gastrointestinal, and genitourinary changes

At least one symptom from three of the following five symptom categories

- Flu-like symptoms may be recurrent or chronic and are typically activated or worsened by exertion e.g., sore throat, sinusitis,
- Cervical and/or axillary lymph nodes may be enlarged or tender with accompanying palpitations.
- Susceptibility to viral infections with extended recovery periods
- Gastrointestinal tract: e.g., nausea, abdominal pain, bloating, irritable bowel syndrome
- Genitourinary: e.g., frequent urge to urinate, incontinence or bladder emptying problem
- Hypersensitivity to food, medicine, odors, or chemicals

> *Notes: Sore throat, tender lymph nodes, and flu-like symptoms are obviously not specific to ME, but their activation in response to exertion is abnormal. The throat may feel sore, dry and scratchy. Color changes can be seen in the tonsils, as an indication of immune activation.*

Energy production/mobility disorders

At least one symptom of the following:

- Cardiovascular
  - Orthostatic intolerance,
  - neurally mediated hypotension,
  - Postural orthostatic tachycardia syndrome,
  - Palpitations with or without cardiac arrhythmias,
  - Dizziness
- Respiratory:
  - air hunger,
  - labored breathing,
  - fatigue of the chest wall muscles.
- Loss of thermostatic stability: e.g.
  - subnormal body temperature
  - significant daily fluctuations
  - Sweating episodes
  - Recurrent feeling of fever with or without low fever
  - Cold extremities.
  - Intolerance to extreme temperatures

1.1.2.1 Checklist for diagnosing ME/CFS according to ICC

At least 3 positive answers to questions 2-5, at least 3 positive answers to questions 6-10, at least 1 positive answer to questions 11-14

Symptom	Yes	No	Uncertain
1. PEM			
2. Cognitive dysfunction			
3. Pain			
4. Sleep disturbances			
5. Sensory/motor disturbances			
6. Flu-like symptoms			
7. Susceptibility to infections			
8. Gastrointestinal problems			
9. Bladder problems			
10. Sensitivity			
11. Cardiovascular disorders			
12. Difficulty breathing			
13. Temperature sensitivity			
14. Difficulties in keeping warm			

1.2. **Probable causes**

1.2.1. Viral activation/infection

The concept of ME/CFS as being caused by viral infections is strongly supported by a large number of cases reported in outbreaks of probable viral origin, the most publicized being outbreaks in Los Angeles[1], Akureyri in Northern Iceland[2], the Royal Free Hospital in London[3], Incline Village in Nevada[4], and in Tapanui, New Zealand[5].

Chronic symptoms following other acute infections are experienced by some patients. These chronic symptoms resemble ME/CFS, and because of this, ME/CFS is probably a chronic illness following an infection[6]. A prospective cohort study tracking 253 patients from the time of acute infection with Epstein-Barr virus, Coxiella burnetii, or Ross River virus found that 28 of the 253 participants met the diagnostic criteria for chronic fatigue syndrome at six months[7]. The phenotype was stereotyped and occurred at a similar incidence after each infection. The syndrome was predicted largely by the severity of the acute illness rather than demographic, psychological, or microbiological factors[7].

In a prospectively recruited cohort of 4,501 college students, 238 developed infectious mononucleosis (IM) and were followed up at six months to determine whether they recovered or met the criteria for ME/CFS[8]. Those who developed ME/CFS did not have any significant baseline differences in stress, coping, anxiety, or depression, but before IM, they had several cytokine markers that were significantly different from those who did not develop ME/CFS[8].

ME/CFS following IM is a severely debilitating disease in adolescents, and although the prognosis seems better than in adults, their condition can fluctuate and significantly impact their health-related quality of life[9].

In a cohort of 280 adults with COVID-19, it was observed that fatigue and neurocognitive dysfunction at a median of four months following initial diagnosis were independently associated with serological evidence suggesting recent EBV reactivation[10]. The study concluded that their findings suggest differential effects of chronic viral coinfections on the likelihood of developing long COVID[10].

Even though EBV is the primary suspect in ME/CFS, others have pointed to the enterovirus family as being the main cause of ME/CFS[11]. During the polio epidemic from 1934 to 1935[1], 60 times as many hospital employees working with polio patients developed a condition with a cluster of symptoms including pain, fever, headache, nausea, sensory disturbances, constipation or diarrhoea, vertigo, photophobia, and double vision. Patients also experienced fatigue when walking short distances, loss of concentration, lapses of memory, and sleep disturbances, very similar to symptoms reported by patients with ME/CFS; 55% of the staff were still off duty six months after the peak of the epidemic[1].

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1.2.2 Neuroinflammation

Neuroinflammation is a common feature in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) affecting 85-90% of all patients yet the underlying mechanism(s) responsible for the initiation and/or promotion of this process is largely unknown. It has been hypothesised to be the central cause of ME/CFS due to failure of the normal function of neuroglia[1]. An animal study has suggested that a protein secreted by herpes virus 4 (Epstein-Barr virus) can change the blood brain barrier and thus initiate the neuroinflammatory reaction[2]. Following the initial stressor event i.e., a viral infection, the inflammatory response moves to the brain through neurovascular pathways or the dysfunctional blood-brain barrier in the central regions of the brain (paraventricular nuclei and hypothalamus. This elicits a chronic neuroinflammation leading to a sustained illness with chronic relapse/recovery cycles[3]. This could help explain the widespread pathophysiology of ME/CFS, the involvement of the hypothalamic/pituitary/adrenal axis[4], the autonomic nervous system, and the sensitivity normal life stressors of physical, cognitive, psychological, emotional, and environmental origin. The hypothalamus connects the nervous system to the endocrine system, regulating both the HPA axis and homeostatic control of body temperature, fatigue, sleep, and circadian rhythms-all disturbed in ME/CFS.

The CNS is supported by glia cells ("glue" in Greek) that make up half the volume of neural tissue and includes microglia astrocytes, oligodendrocytes, and ependymal cells. Under physiological conditions, microglia play a role in development and maturation of the CNS and subsequently serve in immune surveillance as the resting phenotype. The microglia can release pro-inflammatory cytokines, reactive oxygen, and nitrogen species as well as other chemokines in response to pathogens and/or damage associate debris as they change to a proinflammatory phenotype. If overactivated microglia may lead to a neuroinflammatory cascade and may interfere with nerve repair[5,6].

Activated microglia will activate astrocytes and cause these cells to secrete proinflammatory chemokines associated with a loss in neuronal survival and function. Astrocytes also signal the endothelial cells of the brain vasculature resulting in further disruption of the blood-brain barrier, increasing perfusion and facilitating immigration of blood immune cells[7].

Over time, the phenotype of microglia and astrocytes changes to an anti-inflammatory form - M2 and A2 respectively[8]. By virtue of the immune and glial cells' ability to influence the activity of other neuroglial cells, effects thereof can be conveyed to distant parts of the brain[8]. On the functional level, CNS inflammation has been associated with cytokine-mediated sickness behaviour[9], excitotoxicity (Dong et al., 2009) and dysfunctional connectivity within the brain (notably due to synaptic loss and demyelination) (Rao et al., 2012) that leads to CNS dysfunction affecting sleep.

Magnetic resonance spectroscopi has shown metabolic abnormality in different brain areas in MECFS (see reference 11 for full information). Newer diagnostic imaging modalities have been able to demonstrate changes compatible with neuro-inflammation in ME/CFS. Nakatomi compared PET scanning of the brain in nine patients with ME/CFS and 10 healthy controls[10]. They used a ^{11}C-labelled translocator protein analogue and found widespread accumulation in brain areas in

ME/CFS patients, and the level of the inflammatory marker was associated with the severity of neuropsychologic symptoms[10]. Mueller et al used magnetic resonance spectroscopy to show that ME/CFS patients had increased temperature in several brain regions, which was not attributable to increased body temperature or differences in cerebral perfusion[11]. They found correlation between the brain temperature and metabolic signs of inflammation[11].

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1.3 Fatigue

Intractable or chronic fatigue lasting more than 6 months, unrelieved by sleep, is the most common complaint in patients seeking medical attention[1-4]. It occurs naturally during aging and is also an important secondary condition in many clinical diagnoses. The phenomenon of fatigue (fatigue) has been defined as a multidimensional sensation, and attempts have been made to determine possible causes of fatigue[5-10]. Most patients understand fatigue as a loss of energy and the inability to perform even simple tasks without effort. Many medical conditions are associated with fatigue, including lung, cardiovascular, musculoskeletal, and gastrointestinal diseases as well as infections and cancer[5-10].

Fatigue is related to reduction in the efficiency of cellular energy systems found primarily in mitochondria. Damage to mitochondrial components, mainly by oxidation, can impair their ability to produce high-energy molecules such as ATP and NADH. This occurs naturally with aging[9-10] and during chronic diseases, where the production of reactive oxygen species (ROS) can cause oxidative stress and cellular damage, resulting in oxidation of lipids, proteins, and DNA[7-12]. Upon oxidation, these molecules change structurally and sometimes functionally. Important targets for ROS damage are the phospholipid-containing membranes of mitochondria as well as mitochondrial DNA[7].

In patients with chronic fatigue syndrome, there is evidence of oxidative damage to DNA and lipids[10,11] as well as the presence of oxidized blood markers, such as methemoglobin, indicating excess oxidative stress[12]. In addition, oxidative damage to DNA and membrane lipids has been found in muscle biopsy samples from patients with chronic fatigue syndrome[13]. These authors also found increases in antioxidant enzymes, such as glutathione peroxidase, suggesting that this was an attempt to compensate for excess oxidative stress[13]. Chronic fatigue syndrome patients have persistently elevated levels of peroxynitrite due to excess nitric oxide, and this has been suggested to result in lipid peroxidation and loss of mitochondrial function, as well as changes in cytokine levels that exert a positive feedback on nitric oxide production In addition to mitochondrial membranes, mitochondrial enzymes are also inactivated by peroxynitrite, and this may contribute to loss of mitochondrial function[15,16]. Finally, although there are cellular molecules that counteract the excess oxidative capacity of ROS, such as glutathione and cysteine, these are found at lower levels in patients with ME/CFS[17].

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1.3.1 Mitochondrial dysfunction

Metabolic studies indicate differences between ME/CFS patients and healthy controls, with the most consistent findings being in cellular energy generation and oxidative and nitrosative stress[1]. Increased mitochondrial damage, reductions in ATP production and impaired oxidative phosphorylation all point to ME/CFS potentially being a mitochondrial disease. According to Naviaux et al[2], many of the pathways and metabolites that have been found abnormal in ME/CFS are like those of "dauer" (German for *persistence*), a well-studied, hypometabolic state comparable to hibernation that permits survival and persistence under conditions of environmental stress but at the cost of severely curtailed function and quality of life.

The main abnormality in mitochondrial function in ME/CFS seems to be a shift in fuel utilization by reduction in carbohydrate oxidation and a reliance on fat combustion. Like in hibernating animals this seems primarily mediated by an upregulation of several pyruvate dehydrogenase kinases with an impairment of the pyruvate dehydrogenase complex[3]. Others have pointed to impairments in glycolysis in addition to mitochondrial function with lower rates of ATP production across the board[4]. Based on measurements of ATP production by peripheral blood mononuclear cells (PBMCs) in the presence of different concentrations of glucose, it has been speculated that ME/CFS may reduce cellular competency in adapting to changing energetic demands, which would be consistent with an inability to ramp up ATP production upon exertion. A potential molecular explanation for this deficiency was provided by Missailidis et al. who identified potential defects in mitochondrial complex V (ATP synthase) from an analysis of mitochondrial function in immortalized lymphoblasts generated from 51 ME/CFS patients[5].

PDK4 (pyruvate dehydrogenase kinase isoform 4) is expressed ubiquitously in the mitochondrion matrix of tissues with highest expression seen in liver, heart and skeletal muscles. PDK4 is regulated by glucocorticoids, retinoic acid and insulin, and is found elevated with diabetes, fasting and other conditions where fatty acids act as energy source. PDK4 inhibits the mitochondrial pyruvate dehydrogenase complex (PDC) thus contributing to glucose metabolism regulation. Insulin resistance is associated with PDC dysregulation in skeletal muscles and excessive insulin on the other hand downregulates PDK4 expression. PDK4 exerts conservation of glucose as well as three-carbon compounds such as lactate, alanine, pyruvate etc. which serve as substrates for gluconeogenesis and this conservation helps maintain euglycemia during starvation, however, exacerbates hyperglycemia in diabetes.

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1.3.2 Exercise intolerance and post exertional malaise.

Exercise intolerance

It is often claimed that exertional intolerance in ME/CFS mainly results from deconditioning. In line with that, some clinicians think that graded exercise can help exercise intolerance in ME/CFS. However, aerobic capacity is lower in ME/CFS patients than in sedentary control subjects[1] and it has been demonstrated that ME/CFS patients present clinically significant decrease in peak maximal oxygen uptake only on day 2 of exercise testing[1]. Lien et al[2] showed that lactate production per workload was significantly higher in ME/CFS and that the difference was greater on day 2 of the exercise test[2]. The response to a two-day exercise testing differs significantly between patients with idiopathic chronic fatigue and those with ME/CFS with the first group improving and latter group deteriorating on the second day of testing[3]. Deconditioning in otherwise healthy subjects is characterized by low cardiac output at peak exercise4 but the study by Joseph P et al[5] found increased cardiac output in ME/CFS patients. They also noted low cardiac filling pressures in ME/CFS rather than the higher pressures seen in detrained individuals. A recent, deep phenotyping study[4] found previously undescribed dysfunction of brain regions that drive the motor cortex abnormality apparently impeding the voluntary muscle performance.

Even though deconditioning cannot explain exertional intolerance in ME/CFS, it is important to prevent secondary deconditioning by encouraging fitness with a careful, individualised exercise program to help compensate for disease-associated cardiovascular limitations.

Post exertional malaise.

Exertion-induced aggravation of symptoms generally called post-exertional malaise (PEM) is the hallmark of ME/CFS and often described by the patients as a “crash”. PEM is a delayed worsening of any or all ME/CFS symptoms irrespective of whether the exertion is physical, social, mental, or a combination. Focussing on PEM in the clinical situation has significant importance for the outcome in ME/CFS patients. Cross-sectional surveys covering specialist healthcare services for ME/CFS patients in Norway found that PEM was infrequently addressed and that failure to address PEM roughly doubled the risk of health deterioration, following rehabilitation[7].

A study on lactate levels in ME/CFS and healthy controls indicates that previous exercise increases lactate accumulation in ME/CFS as opposed to the reduction seen in healthy controls[8]. This could be one of the mechanisms responsible for PEM and if repeated could cause inflammation and myopathy. It has been found that elevated blood lactate in the resting condition correlates with PEM in ME/CFS[9]. A study in Long-COVID-patients fulfilling the main ME/CFS criterion of PEM has shown that local and systemic metabolic disturbances, severe exercise-induced myopathy, infiltration of amyloid-containing deposits, and immune cells in skeletal muscles were key characteristics PEM which further underlines the importance of limited exercise programs to avoid such pathological and perhaps long-term deterioration of physical function in both ME/CFS and Long-COVID[10].

Characterizing the nature of post-exertional symptom exacerbation is important for developing and evaluating rehabilitation strategies, including the potential benefits or harms of exercise for persons living with ME/CFS. A study by Davenport TE et al[11] indicate clinicians only need to focus on the presence and duration of just a few symptom categories and prolonged duration to identify

its existence. According to that study, inquiring about post-exertional cognitive dysfunction, decline in function, and lack of positive feelings/mood may help identify PEM quickly and accurately. A newly developed questionnaire addresses the consequences of exertion in ME/CFS[12], the premise being that ME/CFS patients can cope with various forms of exertion but at the cost of deterioration in their health for days to months and perhaps even permanently.

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1.4 Quantifying disease impact

1.4.1. Symptom-based questionnaires

1.4.1.1. General health - SF 36

Short Form 36-Item Health Survey or SF-36 is a patient-reported health measure that assesses health-related quality of life in 8 areas: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. A score of zero represents completely disability, and a score of 100 no disability. It is available in many languages including Danish with Danish normative data.

A study including 289 ME/CFS patients diagnose with ME/CFS using the International Consensus Criteria (ICC) and quantified disease impact by SF36, mean number of steps per day, and estimated maximal oxygen consumption. They concluded that using these methods of quantification made the disease impact more comprehensible for the patient and his/her caretakers, treating physicians and authorities[1].

1.4.1.2. General Health - EQ-5D-5L/3L

EQ-5D-5L or 3L is a standardised measure of health-related quality of life developed by the EuroQol Group[2] and assesses health status in terms of five: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; and 5) anxiety/-depression dimensions. The questionnaire is available in Danish and was used in study of ME/CFS-patients in Denmark[3]. Results from the questionnaire was compared to a large Danish study (177,639 included) of health- related quality of life in the general population i.e. both healthy subjects and people with various diseases[4]. The study concluded that the health-related quality of life in patients with ME/CFS is significantly lower than the population mean and the lowest of all the compared other diseases[3]. The adjusted analysis confirms that poor quality of life is distinctly different from and not a proxy of the other included conditions.

A multinational study to assess the impact on the quality of life (QoL) of people with ME/CFS 2022[5]. The study included 1,418 people with ME/CFS and their 1,418 family members/partner from 30 countries.

Impact on quality of life was significantly correlated between those with ME/CFS and their family member. Family members were most impacted emotionally by worry, frustration and sadness and personally by family activities, holidays, sex life and finances[5].

Almost all ME/CFS participants (1,397) had problems performing their usual activities and more than half were unable to perform usual activities at all. Almost 94% experienced pain and discomfort and in one-third, pain and discomfort was classified as extreme. Mobility was affected in 89%, with participants experiencing some problems (1,063) with walking or were confined to bed (193). In terms of self- care,

67% had some problems or were unable to wash or dress themselves. Anxiety and depression were the least affected dimension, 576 participants were not anxious or depressed at all, while 678 were either moderately and 164 were extremely anxious or depressed[5]. The authors concluded that despite the limitations of selection bias in open participation surveys, this research has revealed the significant worldwide burden of ME/CFS on the quality of life of people with ME/CFS and on their family members[5].

1.4.1.3 Functional capacity - FUNCAP

FUNCAP (FC), is a questionnaire primarily developed to accurately assess FC in ME/CFS patients[6]. The questionnaire consists of eight domains divided by activity types: A) personal hygiene/basic functions, B) walking/movement, C) being upright, D. activities in the home, E) communication, F) activities outside the home, G) reactions to light and sound, and H) concentration. A Danish translation is in progress.

Initial testing in 1263 Norwegian and 1387 English-speaking patients showed FUNCAP to be a reliable and valid tool for assessing functional capacity in ME/CFS patients.

1.4.1.4 Fatigue questionnaires

Fatigue Severity Scale

There has been limited research comparing the efficacy of different fatigue rating scales for use with individuals with ME/CFS, but the Fatigue Scale and the Fatigue Severity Scale (FASS)[7] have commonly been used as a measure of the severity of specific fatigue-related symptoms, and to assess functional outcomes related to fatigue, respectively[8]. A comparison between the scales in an ME/CFS-population found FSS to be more accurate and comprehensive measure of fatigue-related severity, symptomatology, and functional disability[8] and a study by the same group found that FSS had the best ability to differentiate ME/CFS from healthy controls[9]. Fatigue severity scale has been validated in Danish[10].

Chalder Fatigue Questionnaire (CFQ)[11] was developed to measure severity of fatigue illnesses and has been used in to study the effect of ME/CFS such as the disputed PACE-trial[12]. In a recent study in a small group of ME/CFS-patients[9], CFQ was described as consisting of one item clearly related to physical symptoms, four items clearly related to cognitive function, and one item relating to fatigue which could be interpreted as cognitive and/or physical fatigue. According to participants, the remaining five questions lacked clarity, were relating to behaviour not symptoms, or relating to sleepiness not fatigue. The CFQ has not been accepted as a tool for research use by the US National Institute of Neurologic Diseases and Stroke[9].

1.4.1.5 Autonomic dysfunction – COMPASS31.

The Composite Autonomic Symptom Score (COMPASS 31) is a validated self-assessment questionnaire quantifying the severity and distribution of autonomic symptoms across six domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor functions) by scoring 31 clinically selected questions[7]. It was developed to detect and quantify the degree of autonomic failure, to

monitor disease progression and to evaluate response to treatment. The total score of the COMPASS 31 questionnaire ranges 0-100 with higher values mirroring more severe symptoms of autonomic dysfunction[14].

The COMPASS 31 questionnaire has been extensively validated in different patient categories and in healthy subjects. A study comparing COMPASS31 in ME/CFS-patients to healthy controls showed that a cut off level in total score of 32.5 was a diagnostic criterion for autonomic dysfunction in CFS patients15. There is some skewing in the number of questions with few addressing orthostatic intolerance and tree times as many focussing on gastrointestinal problems. The National Institute of Neurological Disorders and Stroke rates COMPASS31 as" highly recommended in ME/CFS"[16] but the shortcomings in orthostatic symptoms seem to require further testing. COMPASS31 has been translated and validated in Danish[17].

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1.4.2 Muscle strength and endurance – Hand-grip testing

Maximal exercise performances are characterized by the peak oxygen uptake and the maximal work force, but these procedures will cause post exertional malaise in patients with ME/CFS. A comparative study in 66 ME/CFS-patients[1] concluded that handgrip strength can predict maximal exercise performance in these patients.
Hand-grip dynamometry is recommended to perform in sitting position with the arm flexed at the elbow and cannot be applied to patients following abdominal surgery, musculoskeletal spine or hip injuries[2]. In a population of young healthy subjects, the reproducibility was nearly perfect[2].
Normative data have been determined[3]and can be used for comparisons.
Hand grip strength (HGS) has been used as an objective measure of muscle strength and fatigue in primary symptom of ME/CFS[4]. In a group of 272 British ME/CFS patients, HGS indicators were associated with having ME/CFS, with magnitudes of association stronger in severely affected than in mild/moderately affected patients. The association persisted after adjusting for age, sex and body mass index and there were significant correlations between HGS indicators and clinical parameters of disease severity, including fatigue analogue scales[4]. A study in 105 German ME/CFS patients found that - compared to controls - the patients had a significantly lower strength and that the decline in strength during repeat maximal HGS measurement was significantly higher. Lower HGS parameters correlated with severity of disease, post-exertional malaise and muscle pain and with higher blood levels of creatinine kinase and lactate after exertion.

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1.4.3. Autonomic function

Measurements of autonomic function is primarily based on measurements of cardiovascular control i.e. heart rate and blood pressure responses to different physical challenges such as deep breathing, exhaling against an expiratory resistance (the Valsalva manoeuvre) and changes in position from supine to upright.
Quantitative sweat test is also used in some laboratories to detect abnormalities in the small nerve fibres of the peripheral autonomic nervous system.

1.4.3.1. **Tilt-testing and Valsalva manoeuvre**

In tilt testing the subject is place in the supine position on tilt-table and heart rate and blood pressure are recorded continuously in a non-invasive manner. After resting for at least 10 min in the supine position the table is tilted to 60 degrees head-up position. At this tilt angle the body is submitted to 90% of the gravity force attained in the full upright position. Dependent on the diagnostic purpose the subject remains in this position for 10 to 45 min. in the tilted position the force of gravity causse a displacement of blood from the upper to the lower body compartments causing a reduction in cardiac filling pressure. As a consequence, there is an immediate reduction in cardiac stroke volume and hence in blood pressure which is initially compensated by an increase in heart rate an within the first minute followed by peripheral vasoconstriction increasing blood pressure and causing heart rate to return to a level 10-20 beats per minute higher than in the supine. Tilt testing has been widely covered in consensus satetments[1,2,3].
In the Valsalva manoeuvre the subject is place in a sitting position with continuous measurements of heart rate and blood pressure. After a 5 min resting period the participant is asked to take a deep breath and then exhale through a mouth piece connected to an aneroid manometer keeping the expiratory and hence the intrathoracic pressure at 40 mmHg for 15 seconds and then exhale without resistance and breath normally for 2 min. Then increased intrathoracic pressure reduces the cardiac filling pressure causing the blood pressure to fall and the heart rate to increase and in healthy subjects, constriction of the peripheral vasculature then causes blood pressure to return the level prior to the manoeuvre. At release of the expiratory pressure blood pressure falls shortly before reaching a higher level (overshoot) as cardiac filling is normalised and the heart is pumping against an increased vascular resistance this sequence of events allowing for calculation of the baroreceptor sensitivity and for extraction of the activity in the parasympathetic and sympathetic divisions of the autonomic nervous system[4]. The response can also be classified in different categories relating to the degree of dysfunction in the autonomic nervous system[5]

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1.4.2.3. **Heart rate variability**

Heart rate is tightly controlled to adapt to the demands of the body and therefore show characteristic oscillation over time. There is a diurnal variation with lowest heart rate in the middle of the sleeping period under normal circumstances. Heart rate also varies from beat to beat – oscillations than are commonly referred to as heart rate variability (HRV).
In testing HRV is important to differentiate between variation caused by specific physiological manoeuvres such a deep breathing or active change in posture from supine to standing and the spontaneous variation seen over limited time periods in the resting supine or sitting positions. HRV can also be measured over 24-hour periods or longer.

The strongest oscillations in heart rate are driven by breathing[1] and the largest difference in heart rate in response to breathing is attained at a breathing frequency of 6 respirations per minute[1]. The variations in heart rate during deep breathing are initiated primarily by the parasympathetic nervous system through the vagal nerve and forms the basis for breathing techniques used to reduce mental stress. The other strong oscillator causing HRV is the blood pressure control system. The activity of the two principal oscillators can be quantified through analysis of the frequency component embedded in HRV – practically separated into high and low frequency component, where the high frequency component (HF) is commonly equated with parasympathetic activity and the low frequency component (LF) represents the sympathetic activity. The ratio between LF can then be equated to the balance between the two components of the autonomic nervous system[3]. A Danish study on normative values for HRV has been published[4].

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Section 2: Treatment

2.1 Mitochondrial Dysfunction

2.1.1. Co-enzyme supplementation

Coenzyme Q_{10} - also called Ubiquinone - is produced in the body and can be obtained from dietary source mostly localized in the mitochondria. Q_{10} is primarily located in the mitochondria and together with nicotinamide adenine dinucleotide in the oxidized form (NAD+ or the reduced form NADH), Q_{10} is a key component of the electron transport chain responsible for mitochondrial energy production in the form of ATP. Q_{10} also acts as an antioxidant[1] through removal of reactive oxygen species i.e. unstable molecules that may oxidize and hence damage other molecules in the cell including the DNA. After acting as an antioxidant, Q_{10} must be reduced via NADH-related enzymes to be reactivated. Q_{10} is a product of the cholesterol synthesis in the liver, and it has been shown that statins significantly reduce Q_{10} levels[2].

NAD+/NADH is critically involved in the mitochondrial ATP production together with Q_{10} and can be synthesized from a multitude of precursors from the normal human diet – the most prominent collectively known as B3-vitamin (niacin/nicotinamide). Normal dietary intake of NAD+/NADH precursors is estimated to be 20-40 mg/day and stems from both animal and plant-based diets[3].

A recent meta-analysis of Q_{10} supplementation in the general population[4] found that it can reduce inflammatory mediators and that the optimal daily dose seemed to be 300–400 mg.

A recent review of supplementation with NAD+/NADH[5] in different conditions including CFS found that their study supported that oral administration of NADH I doses of 5 - 80mg/day can lead to an increase in quality of life and improvements in health parameters. They also found that NADH supplementation is safe with a low incidence of side effects.

A prospective randomized, placebo-controlled trial[5] of the combination of Q_{10}/NADH in doses of 200/20mg in 207 ME/CFS patients found reduction in cognitive fatigue perception and overall using the Fatigue Impact Scale and an improvement in health-related quality of life from baseline. Significant differences were also shown for sleep duration at 4 weeks and habitual sleep efficiency at 8 weeks in follow-up visits from baseline within the experimental group. In a previous study, the same group found significant reductions in max HR during a cycle ergometer test combined with a decrease in perception of fatigue in the active group compared to placebo. Both studies found that the combination of Q_{10}/NADH were well tolerated with no serious side-effects.

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2.1.2. Antioxidants

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a dual role in being both deleterious and beneficial. ROS and RNS are normally generated by tightly regulated enzymes and overproduction results in oxidative stress which causes damage to cell structures, including lipids, membranes, proteins, and DNA. In contrast, ROS/RNS exerts beneficial effects at low/moderate concentrations as - for example - defenses against infectious agents[1]. The reactive oxygen species are counterbalanced by enzymatic and non-enzymatic antioxidants. Enzymatic antioxidant defenses include - among others - superoxide dismutase, glutathione peroxidase, and catalase. Non-enzymatic antioxidants are represented by vitamin C, Vitamin E, glutathione (GSH), carotenoids, and flavonoids. Q_{10} also has important antioxidant properties as has selenium and selenium is an important component of enzymatic antioxidants[2]. Oxidative stress denotes a shift towards increases in reactive oxygen species relative to antioxidant defense mechanisms and is a hallmark of mitochondrial dysfunction in ME/CFS[3,4]. Several studies have shown aberrations in metabolism of lipids, in the redox balance and in energy production in ME/CFS[3,4,5,6], probably caused by defects in the pyruvate dehydrogenase complex[4] – an essential key in the aerobic glucose metabolism.

Vitamin C (ascorbic acid/ascorbate) is a potent antioxidant, important for the formation of biogenic amines and contributes to immune defense. Infections significantly impact vitamin C levels due to enhanced inflammation and metabolic requirements. Fatigue, pain, cognitive disorders, and depression-like symptoms are known symptoms of vitamin C deficiency[7]. Vitamin C concentrations are tightly controlled with oral ingestion in healthy subjects with dose-independent plasma levels at intakes of more than 1.000 mg/day. To achieve higher plasma concentration, intravenous administration (iv) is necessary[8]. A placebo-controlled study of iv C-vitamin in healthy subjects found significantly lower measures of oxidative stress and a positive effect on fatigue. There were no differences in adverse events or side-effects between active and placebo treatment.

Selenium

Selenium (Se) is an essential trace element and has an important role as part of several selenoproteins with critical roles in thyroid hormone metabolism, DNA synthesis, reproduction, and protection from oxidative damage and infection. In foods, Se is predominantly present as selenomethionine, which is an important source of dietary Se in humans, and as a chemical form that is commonly used for Se supplements in clinical trials. Daily recommended dose of Selenium in healthy subjects olde than 14 years of age is 55 microg daily. The upper tolerable limit is 400 microg in the same age group[9]

Concern for potential deficiency diseases associated with low Se status has led to the establishment of the recommended daily requirements for Se in many countries. Excess Se intakes through supplementation and its potential misuse as health therapy could also pose a risk of adverse health effects if its use is not properly regulated.

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2.4. Treatment of neuroinflammation: Dietary supplements.

2.1.1 Palmitoylethanolamide (PEA)

PEA is a food component first discovered in the late 1950s and shown to have anti-allergic and anti-inflammatory activity[1]. PEA is an endocannabinoid, and it selectively stimulates the cannabinoid CB2 receptor avoiding the hallucinogenic effects of stimulating the CB1 receptor. It is generally accepted that PEA has a multitargeted action and – important in the treatment of ME/CFS and related conditions – an ability to reduce inflammation, pain, mast-cell activation, and experimental colitis[2].

Pharmacological properties: Because of the lipidic nature and large particle size, PEA has to be micronized to give a better adsorption. Experimental inflammation has been shown to be reduced by oral treatment with micronized and ultramicronized PEA whereas the nonmicronized PEA had no effect[3]. The plasma elimination half-time of PEA is 12 min in the rat[4] and most of the PEA is located in the extravascular compartment. PEA is found in the brain, with a preferential retention in the hypothalamus where CB2 receptors are present[5].

Effect on inflammation and mast-cell activation: PEA has been reported to decrease the release of several pro-inflammatory cytokines and that PEA has a curative effect in a model of acute inflammation[6]. In the brain PEA selectively binds to the cannabinoid CB2 receptor which is abundantly present on human microglia cells which would account for the possible beneficial effect of PEA in conditions of neuroinflammation. It has been suggested that chronic inflammation might develop because of low endocannabinoid tissue concentration and that a correction of this could be exploited to develop new anti-inflammatory drugs[7]. Recently, PEA has been reported to down-modulate mast cell activation in vitro by behaving as an agonist at the peripheral cannabinoid CB2 receptor[8].

Tolerability of PEA: The current clinical data indicate that there are no ‘very common’ or ‘common’ serious adverse reactions but there is insufficient data to give information in the ‘uncommon’ or ‘rare’ categories[4]. The DTU Food Institute has assessed that no harmful effects of PEA have been reported and that based on data from experimental studies, a safe intake of 5 mg/kg body weight per day for PEA can be calculated[9].

Effect on pain: A meta-analysis of double-blind, controlled, and open-label clinical trials has shown that PEA elicits a progressive reduction of pain intensity significantly higher than control with the effects being independent of patient age or gender, and not related to the type of chronic pain[10]. A large observation study on 600+ patients from a single pain clinic has shown that PEA significantly reduces pain when added to usual analgesic therapy[11]. A meta-analysis of six randomized, placebo controlled, clinical trials point to efficacy of PEA over placebo and when compared to NSAID the effect of PEA lasted longer than that of NSAID[12].

The proposed mechanism(s) of action of PEA involve – among others - the effects upon mast cells[13] and CB2-like cannabinoid receptors[14].

Practical approach: Most of the studies have used a total daily dose micronized PEA of 800 to 1.200 mg. In clinical experience from 500+ patients this is a highly tolerable dosage, and the onset of effect is to be expected within (several) weeks.

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2.1.2 Pycnogenol

Pycnogenol is extracted from the bark of a French pine tree (Pinus pinaster) and the main components are procyanidins (70+/- 5%) and their monomers (catechin and epicatechin) as well as phenolic acids[1]. Pycnogenol is safe for use in conventional foods, based on the evaluation of clinical safety and preclinical toxicology data by an independent panel of toxicology experts. Non-mutagenicity, lethal dose (LD50) > 5.0 g/kg body weight, the no adverse event level has been determined at > 1,000 mg/kg/day [*2*], and this translates in a safe dosage of > 700 mg/day. Typically, oral dosages tested in the literature are in the 30–200 mg/day range, with some studies exploring higher dosages of 200–450 mg/day. Since it was introduced into the market in Europe around 1970, there have been no reports of serious adverse effects in any clinical study or from commercial use of Pycnogenol. Mild side-effects of gastric discomfort have rarely been reported and linked to stomach-sensitive patients. No interactions of Pycnogenol with other drugs, alcohol or food intake have been reported[2].

Endothelial function: Sandvik MK et al has shown that ME/CFS patients have reduced macro- and microvascular endothelial function, indicating that vascular homeostasis may play a role in the clinical presentation of this disease[3]. A study by Newton et al.[4], investigating flow-mediated dilation (FMD) for large vessel endothelial function and post-occlusive reactive hyperemia (PORH) for microvascular function in ME/CFS patients, concluded that ME/CFS patients have both large and small vessel endothelial dysfunction as compared to age- and sex-matched controls[4,5]. Clinical studies have showed that Pycnogenol can improve endothelial function[6,7]. The suggested mechanism of action is activation of the endothelial nitric oxide synthase amplifying the NO generation from L-arginine, eventually leading to an increase in vessel lumen and adequate tissue perfusion[7].
Micro-clots and associated coagulation issues have been found present in ME/CFS and point to a systemic vascular pathology and potential endothelial inflammation and targeted therapies to address vascular and endothelial pathology might has been suggested[8].
Pycnogenol lowers blood platelet aggregation as effectively as aspirin, without increasing the bleeding time[9,10]. Pycnogenol prevents platelet hyperactivity but does not influence bleeding time, unlike aspirin[9].
Antioxidant activity of Pycnogenol has been investigated in several clinical studies[11] and has been shown to increase the plasma antioxidant capacity and decrease the plasma oxidative stress.
Practical approach: Treatment with Pycnogenol is recommended at a morning dose of 200mg. Besides hypersensitivity to pine bark there are no known contraindication to Pycnogenol. Presently, documentation of the optimal duration of treatment and the long-term effects is lacking[12].

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2.2 Treatment of neuroinflammation, medical treatment

2.2.1 Medical treatment: Low dose Naltrexone (LDN)

Naltrexone is an opioid receptor antagonist and in low doses (0.4 to 4.5 mg) it has both analgesic and anti-inflammatory effects[1,2,3] and is referred to as Low-dose naltrexone (LDN). LDN has been used off-label for treatment of pain and inflammation in multiple sclerosis, Crohn's disease, fibromyalgia, and other neuro-pathic/-inflammatory conditions and current evidence supports the safety and tolerability of LDN in these illnesses[1,2,3]. Studies on quality of life and self-reported pain demonstrate that LDN has subjective benefits over placebo[1,2,3]

Naltrexone is almost completely absorbed orally but the bioavailability ranges between 5 and 40 per cent. The half-life elimination is 4 hours, and it is excreted primarily in the urine, but no dosing adjustments are needed in mild renal impairment[1].

Studies have indicated that LDN has a damping effect on the immune cells in the central nervous system and counteract the proinflammatory activation that occurs in response to pain[2] and leads to a reversal of neuropathy[3]. A retrospective review on LDN in 215 patients with multiple sclerosis found that 77% of the participants had no side effects and no participants were hospitalized from adverse events by LDN. The primary indication was LDN, and this was reduced in approximately 60%. 75% of the participants reported perceiving an increased or stabilized after LDN therapy.

A similar study in 218 patients with ME[5] reported on safety and effectiveness data of LDN in dosages of 3.0 – 4.5 mg/day. The retrospective analysis of medical records showed positive response in 74% experiencing improved vigilance/-alertness, improved physical and cognitive performance. Some patients reported less pain (17%) and fever (15%), while 18% had no response. Mild adverse effects (insomnia, nausea) were common at the onset of the treatment. Neither severe adverse effects nor long-term adverse symptoms were reported[5].

A randomized, double blinded study of LDN in 31 women with fibromyalgia found significant, reduction of pain compared placebo. LDN was also associated with improved general satisfaction with life and with improved mood. Thirty-two percent had significant reductions in pain and in either fatigue or sleep problems contrasted with an 11% response during placebo. LDN was rated equal to placebo in side-effects, and no serious side effects were reported.

Practical approach: Due to the unpredictable bioavailability in the individual patient it is recommended to up-titrate the dose slowly starting with 0.5mg with stepwise increases of 0.5 mg every third week to a maximum of 4.5mg. Should side effects appear the patient could go one step back and try to proceed with the stepwise increments after three weeks or if there is an effect at a lower dose the stay at that level.

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3. Antiviral treatment

3.1. Valacyclovir

Acyclovir, ganciclovir, and famciclovir are nucleotide analogue inhibitors which inhibit viral replication during DNA multiplication or RNA multiplication[1]. Valacyclovir is a valine derivative of acyclovir and is well absorbed from the gastrointestinal tract where it is converted to acyclovir[2]. Valganciclovir is – like valacyclovir - a valine derivative improving the absorption from the gastrointestinal tract. Valganciclovir is commonly reserved for preventing and treating cytomegalovirus-infections in immunosuppressed individuals. Famciclovir is readily absorbed but does not seem to offer superiority to Valacyclovir[3] and - as is the case with valganciclovir – far more expensive.

A study in 25 ME/CFS patients has evaluated the safety and efficacy study of valacyclovir given at 1,000 to 1,500 mg every 6 hours a day for 6 months[4] and this dose achieved serum acyclovir levels to have a high antiviral activity versus Herpes virus 4 (EBV). The authors concluded that the 16 ME/CFS patients with persistent infection EBV-infection improved after 6 months of continuous dosing with valacyclovir. Nine ME/CFS patients with Herpes virus 5 (CMV) co-infection did not benefit from 6 months of similar treatment.

Safety monitoring data from clinical trials of valacyclovir, involving over 3,000 immuno-competent and immunocompromised persons receiving long-term therapy for Herpes Simplex Virus (HSV) suppression, were analysed[5]. Safety profiles of valacyclovir ($\leq$ 1,000 mg/day), acyclovir ($\leq$ 800 mg/day), and placebo were similar. Extensive sensitivity monitoring of HSV isolates confirmed a very low rate of acyclovir resistance among immunocompetent subjects ($\leq$ 0.5%)

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4. Autonomic dysfunction

A significant minority of patients experience symptoms compatible with dysfunction of the autonomic nervous system, including orthostatic intolerance (POTS), gastrointestinal disturbances, bladder dysfunction, and circulation issues.

Using the Composite Autonomic Symptom Scale (COMPASS[1]), a study in ME/CFS found that symptoms of autonomic dysfunction were strongly and reproducibly associated with the presence of ME/CFS[2]. They also found a reverse correlation between low frequency variation in heart rate variability and the COMPASS score Studies in ME/CFS have compared results from the COMPASS questionnaire and data on heart rate variability HRV and have found A high COMPASS score correlated to a significant negative correlation between LF-HRV and COMPASS scores[2]

In a case–controlled study of 45 female patients and 25 age- and gender-matched healthy controls[3] it was found significant relationships between self-reported fatigue symptoms and indices of heart rate variability in patients with ME/CFS[3].

4.1. Postural tachycardia syndrome (POTS)

POTS denotes a condition where heart rate increases by more than 30 beats per minute on assumption of the upright posture in subject older that 18 year of age and more than 40 beats per minute in the younger age group. Heart rate increases of that magnitude i.e. postural tachycardia can been seen in dehydrated subject and in astronauts returning after longer periods in space where they are not submitted to gravity – the most important signal to fluid retention in humans. POTS is diagnosed if the abnormal hemodynamic measures are accompanied by returning symptoms of dizziness, nausea, near fainting, cognitive impairment and other symptoms related to the upright posture[4].

A study in ME/CFS patients with POTS showed that patients in this subgroup were significantly younger, had a shorter length of illness, experienced greater task difficulty and were able to stand for significantly shorter periods compared to those ME/CFS-patients without POTS.

The probable cause for POTS in ME/CFS is most likely and inability to contract the peripheral vasculature during orthostasis and are thus dependent on increments in heart rate to keep blood pressure at a level that ensures an adequate perfusion pressure for the cerebral vasculature. It has also been shown that POTS patients have low frequency oscillations in heart rate and blood pressure[6]. A study simulating such oscillations in healthy subjects using lower body negative pressure demonstrated that healthy subject developed brain fog during such oscillations[7].

Treatment of POTS[4] is directed at reducing the fluid displacement during the upright posture by increasing the intake of salt and fluid - 1 g of NaCl pr liter of fluid, reducing the tachycardia both in the supine and upright position with adrenergic beta-blockers, muscarinic agonists like Mestinon, and enhancing vasoconstriction with an adrenergic alpha-agonist – Midodrine. Fluid retention can be amplified by Fludrocortisone and/or a vasopressin analogue.

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