Fatigue and Rare Neuroimmune Disorders

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Disclosures

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Fatigue is a difficult subject to investigate due to…

- The lack of a precise definition
- Confusing terminology
- Its subjective nature with no reliable, objective, measurable behavioral surrogate
- Its significant overlap with apathy, depression and sleepiness

Kuppuswamy, A., Brain, 2017

Definition

Fatigue: **<u>Subjective</u>** *perception of* lack of physical and/or mental energy perceived by the individual that interferes with usual or desired activities

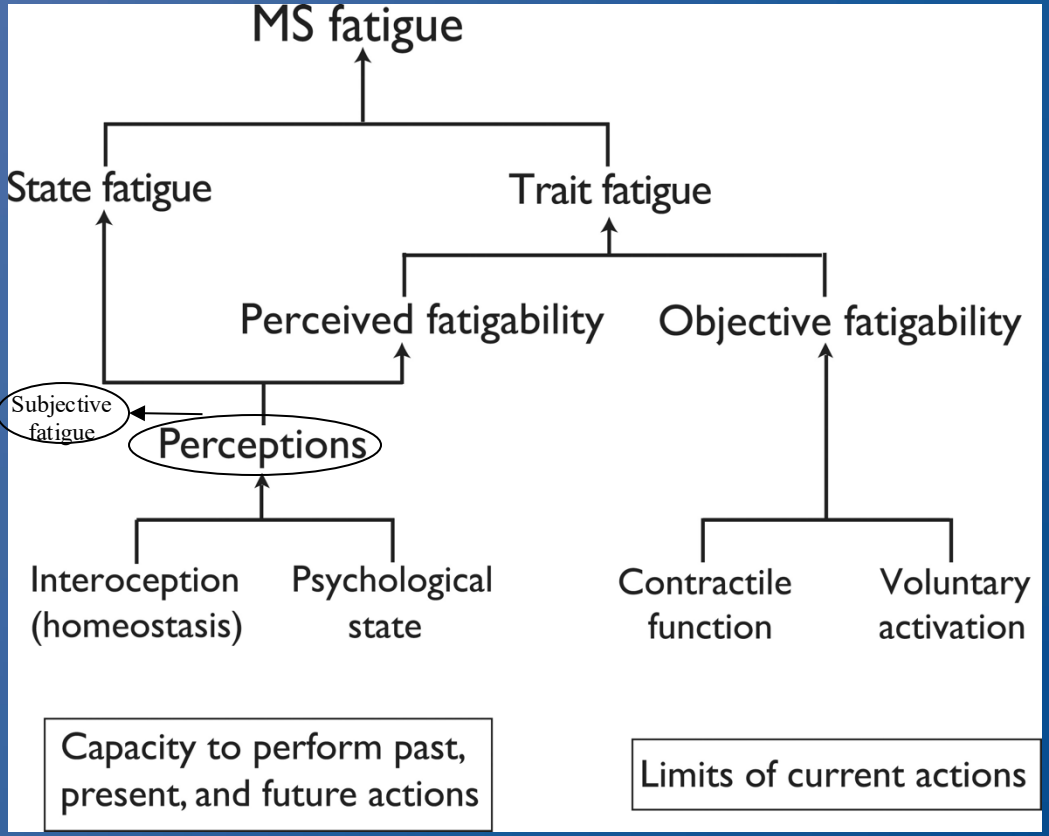
Multiple Sclerosis Clinical Practice Guidelines, 1998

Concepts related to fatigue

Fatigue	**Feelings of tiredness, lack of energy, low motivation, and difficulty in concentrating**
Fatigability	A measure of physical or cognitive work capacity
Objective fatigability	Magnitude of the change in a performance metric after completing a prescribed task
Perceived fatigability	Subjective estimate of past or future work capacity
State fatigue	An instantaneous estimate of the level of fatigue (feelings)
Trait fatigue	A characteristic that can be quantified with measures of either objective or perceived fatigability

Enoka RM et. al., Neurorehabilitation and Neural Repair., 2021

Concepts related to fatigue



Enoka RM et. al., Neurorehabilitation and Neural Repair., 2021

Fatigue and Neuroimmune Disorders

- Most of our knowledge comes from studying fatigue in multiple sclerosis (MS)
- Fatigue is the most common symptom of MS
- Results in loss of employment, reduced quality of life
- Associated with future worsening of disability

Manjaly ZM, et. al., JNNP, 2019; Marchesi S, et. al., Eur J Neurol., 2020; Rommer PS, et. al., MSJ, 2019; Janardhan V. et. al. J Neurol Sci., 2002; Smith MM. et. al. MSJ., 2005; Vaughn CB. Et. al., MSJ, 2018

Epidemiology of fatigue in MS

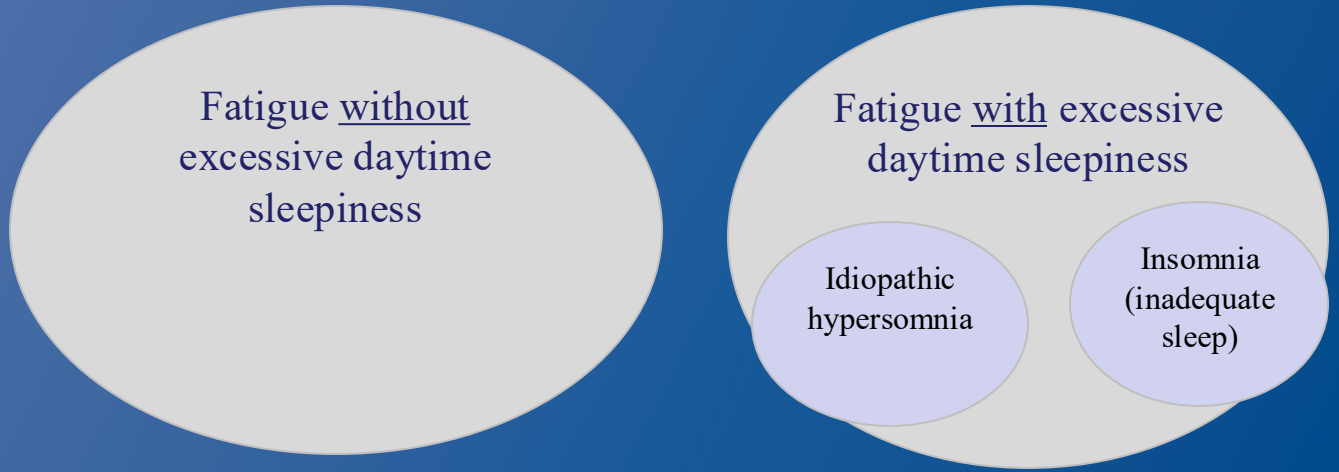
The most common symptom of MS

Present in the earliest stages of the disease, even before cardinal MS symptoms

Perhaps more common in progressive MS and in more disabled patients

Manjaly ZM, et. al., JNNP, 2019; Marchesi S, et. al., Eur J Neurol., 2020; Rommer PS, et. al., MSJ, 2019

Fatigue with and w/o Excessive Daytime Sleepiness



Dubessy AL, et. al. Neurology, 2021

Pathophysiology of MS Fatigue

An extremely multifactorial pathophysiology

More than 30 pathophysiological pathways have been associated wityh fatigue in MS

Langeskov-Christensen M. et.al. J Neurol Sci., 2002, 2017

Pathophysiology of MS Fatigue

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Primary fatigue

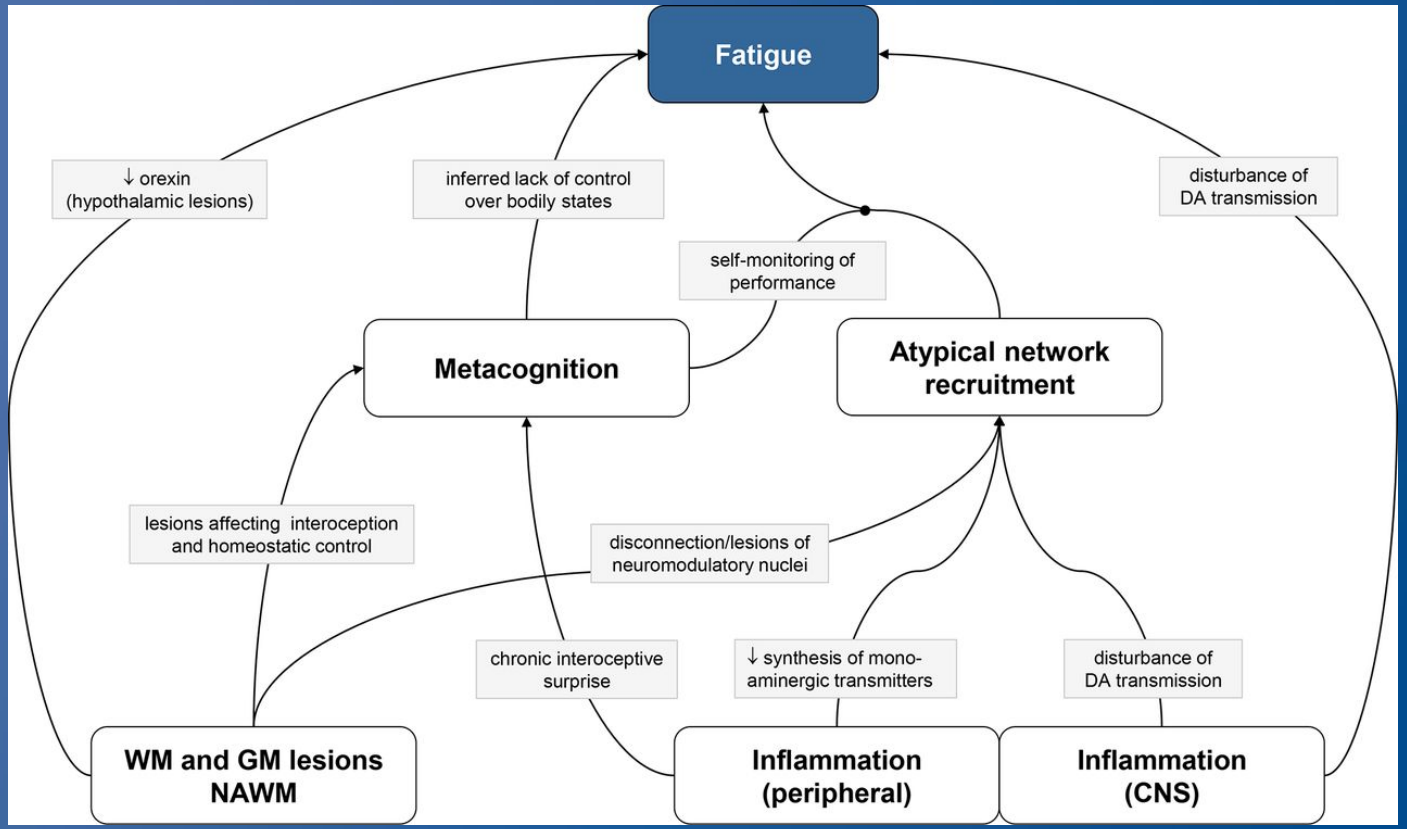
1. Central nervous system pathways
   - Cerebral hypometabolism
   - Cerebral hypoperfusion
   - Brain atrophy (regional/whole brain)
   - Diffuse axonal damage/lesion load
   - Altered cerebral function
     1. Increased cortical excitability and decreased cortical inhibition
     2. Cortical functional reorganization
     3. Impaired cortico-subcortical interaction responsible for motor planning and execution
     4. Basal ganglia system dysfunction affecting integration and cortical feedback through striato-thalamo-cortical fibers
     5. Inadequate increase in cortical activation to compensate for changes in voluntary activation
   - Poor central respiratory control
   - Site of lesion: pyramidal tract damage
   - Autonomic dysfunction
   - MS subtype
   - Afferent pathways failing
   - "The dopamine imbalance hypothesis"
   - The Toll-Like Receptor Radical Cycle Pathway
2. Immunological pathways
   - Activation of pro-inflammatory cytokines
3. Neuroendocrinological pathways
   - Hypothalamic–pituitary–adrenal axis dysfunction

Secondary fatigue

4. Psychological and cognitive pathways
   - Increased subjective fatigue via increased perception of effort.
   - Depression
   - Anxiety and negative affectivity
   - Helplessness
   - Neurotransmitter dysregulation (serotonergic pathways)
   - Stress
   - Sustained cognitive activities
5. Peripheral pathways
   - Decreased isometric and isotonic strength relative to healthy controls.
   - Structural/microscopic muscle changes
   - Oxidative and nitrosative stress (O + NS) pathways
6. Other secondary pathways
   - Sleep disorders
   - Chronically reduced activity/physical deconditioning
   - Iatrogenic mechanisms (medication side-effects)
   - Heat/temperature
   - Pain
   - Lower oxidative capacity in the muscle

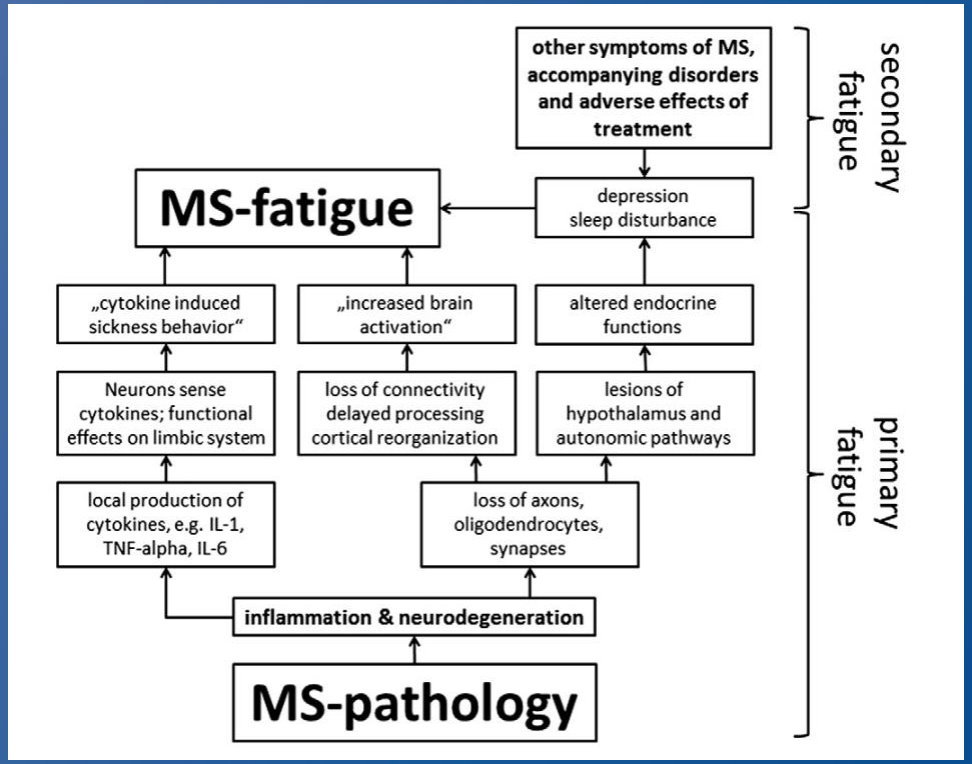
Langeskov-Christensen M. et.al. J Neurol Sci., 2017

Pathophysiology of MS Fatigue



Manjaly ZM, et. al., JNNP, 2019

Pathophysiology of MS Fatigue



Patejdl R. et. al. Autoimmunity Reviews, 2016

Diagnosis and measurement of MS Fatigue

Fatigue is, by definition, a subjective symptom!

The gold standard measure is what the person tells you!

Objective measures should be tested and validated against the gold standard!

Treatment of MS Fatigue:
A neurologist perspective

Despite the prevalence and impact of fatigue, it is vastly undertreated!

In a cross-sectional survey of people with MS on the UK MS Register, 90% of participants reported fatigue

Of those, only 31% reported having been offered any treatment for fatigue

Picariello F. et. al., MSJ-ETC, 2022

Treatment of MS Fatigue:

A neurologist's perspective

Pharmacotherapy

Cognitive-Behavioral Therapy

Exercise

Energy conservation, cooling

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Pharmacotherapy (DMTs)

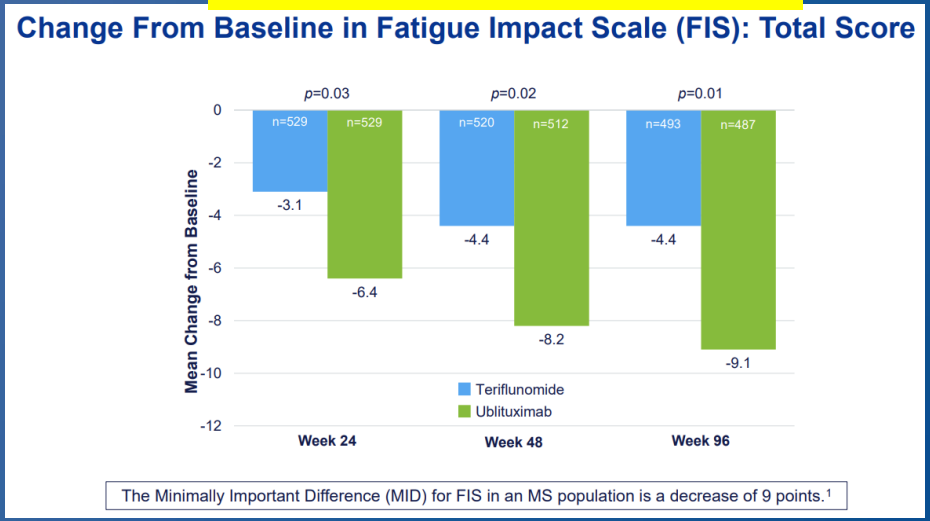
- The role of immune-based disease-modifying therapies in MS fatigue:
- Mostly observational data (confounded by placebo response)
- Improvement of fatigue by some DMTs (such as natalizumab)
- Superiority of some DMTs over others (glatiramer being better in improving fatigue as compared to interferon beta)
- No effect of DMTs on MS fatigue

Svenningsson A., et. al., PLoS One, 2013; Metz LM., JNNP, 2004; Broch L. ,et. al., MSARD, 2023

Pharmacotherapy

- Data from the pivotal trials of recently-approved DMTs:

Ublituximab vs. Teriflunomide

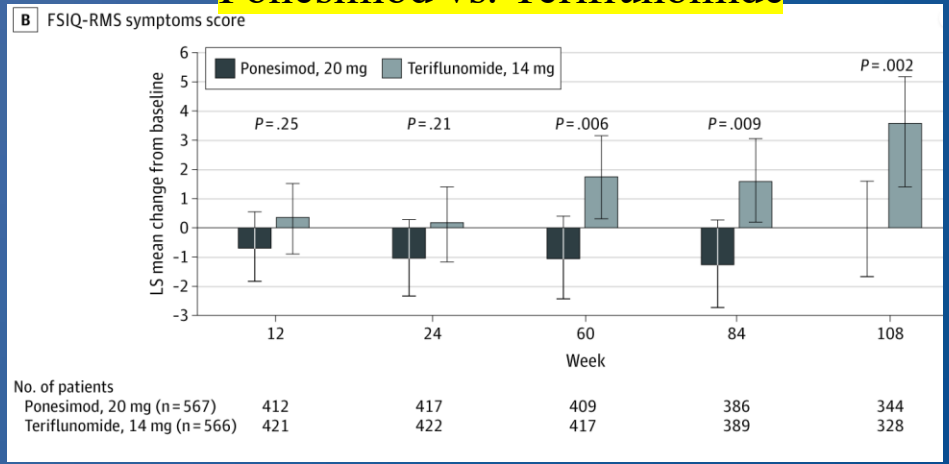


Alvarez E. et. al. CMSC presentation, 2022

Pharmacotherapy

- Data from the pivotal trials of recently-approved DMTs:

Ponesimod vs. Teriflunomide



Kappos L., et. al. JAMA Neurology, 2021

Pharmacotherapy
(symptomatic treatments)

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- Amantadine
- Modafinil and armodafinil
- Amphetamine-like stimulants
- Acetyl L-carnitine
- Fampridine

Pharmacotherapy (symptomatic treatments)

- TRIUMPHANT-MS trial:
  - Amantadine, modafinil, and methylphenidate were not superior to placebo in alleviating fatigue in MS.
  - Amantadine, modafinil and methylphenidate were associated with more frequent adverse events (including moderate and severe) than placebo.

	Measure	Mean Score	Estimated Mean Score				
		Baseline	Placebo	Amantadine	Modafinil	Methylphenidate	P-value for the overall medication effect #
Primary outcome	MFIS Total	51.3±1.2	40.6±1.2	41.3±1.2	39.0±1.2	38.6±1.2	0.20
Secondary outcome	NeuroQoL Fatigue T-score	58.5±0.5	53.1±0.6	53.0±0.6	52.5±0.6	52.0±0.6	0.42

Nourbakhsh B. et. al., Lancet Neurology, 2021

Non-pharmacological Interventions

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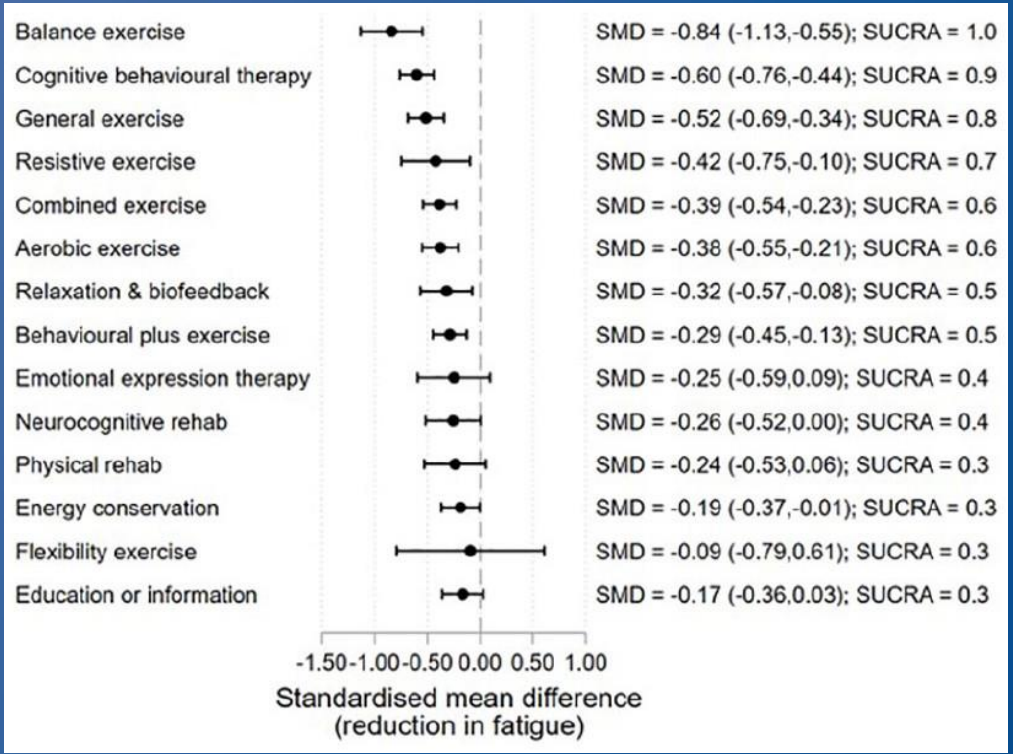
A network meta-analysis of exercise and behavioral interventions for MS fatigue



Harrison AM., et. al., MSJ, 2021

What about fatigue in Rare Neuroimmune Disorders?

- Compared to people with MS, people with NMO had numerically lower fatigue scores, (but the difference was not statistically significant.
- Fatigue is more common in NMOSD (as compared to healthy controls) and correlates with sleep disturbance, daytime sleepiness, and depression.

Chanson JB et. al., European Journal of Neurology, 2010; Pan J. et. al., CNS Neuroscience and Therapeutics, 2015;

What about fatigue in Rare Neuroimmune Disorders?

- In patients with AQP-4-Ab, fatigue was associated with age, disease duration, number of clinical attacks , disability, pain interference, anxiety, and depression
- In patients with MOG-Ab, fatigue was associated with pain interference score and anxiety
- Fatigue was more severe in AQP-4-Ab patients compared to MOG-Ab patients, but the difference was driven by the differences in age, disability and pain interference rather than antibody subtype itself

Yeo T, et. al., ACTN, 2020

What about fatigue in Rare Neuroimmune Disorders?

- While age, disease duration, and annual relapse rate showed no effect on reduced HRQOL in NMOSD, anxiety, disability, fatigue, and depression were independent predictors of poor HRQOL
- Brain functional and structural connectivity changes are associated with fatigue in NMOSD
- Brain structural, diffusion, and functional connectivity alterations related to fatigue are similar among people with MS AQP-4-Ab, and MOGAD
- In MOGAD, fatigue is more severe than healthy controls, and higher age, history of bilateral optic neuritis, and current use of acute treatment were associated with higher fatigue

Shi Z., et. al., J Neuroimmunology, 2020; Zhang Y., et. al., BMC Neurology, 2022; Camera V. et. al., Brain Communications, 2023; Ladakis DC, et. al. MSJ-ETC, 2022

Fatigue treatment in Rare Neuroimmune Disorders

- No evidence-based option!
- Carnitine and IL-6 inhibition were reported ineffective

Fatigue treatment in Rare Neuroimmune Disorders

- Following insight from MS literature!
- Thorough evaluation and treatment of secondary (correctable) causes of fatigue, including medications, sleep disorders and depression.
- Non-pharmacological treatments:
  - Exercise
  - CBT
- Considering pharmacotherapy in patients with concomitant daytime sleepiness:
  - Modafinil
  - Amphetamine-like stimulants

Future Directions

Paying attention to and measuring chronic, invisible symptoms in rare neuroimmune disorders

Rigorous clinical trials for symptomatic therapy in patients with rare neuroimmune disorders

Thank you!