Patient-Reported Outcomes Measures for Multiple Sclerosis: Patient Insights on Fatigue, Cognition, Pain and Depression, and their Interconnectivity

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Introduction

- Fatigue, cognitive impairment, depression, and pain are highly prevalent symptoms in multiple sclerosis (MS) and can negatively impact quality of life in people living with MS (PlwMS)[1-4]
- These symptom domains often co-occur and are interconnected[1-4]
- A better understanding of the interconnected nature of these symptomatic domains, as well as potential associated unifying biological mechanisms, may help to inform the development of targeted behavioral and pharmacological interventions
- Furthermore, such knowledge may help to inform the development of patient reported outcome (PRO) measures that capture the experience of PlwMS in more accurate and meaningful ways than existing measures

Objectives

1. To quantify the co-occurence of fatigue, cognitive impairment, depression, and pain among a large sample of PlwMS, and the impact of these symptoms on quality of life
2. To elucidate insights from a group of MS patient experts on the interconnected nature of fatigue, cognitive impairment, depression, and pain based on their experience of the disease
3. To identify potential underlying biological processes that may explain the interconnected nature of fatigue, cognitive impairment, depression, and pain in PlwMS, based on a literature review

Methods

Living Like You (LLY) Survey

- Online survey of 2,052 PlwMS from 23 different countries
- Designed to quantify the co-occurence of fatigue, cognitive impairment, depression, and pain, and the impact of these symptom domains on quality of life (QoL)
- Participants responded to the following questions using a 5-point Likert scale, whereby 1 represented 'not at all impactful' and 5 represented 'extremely impactful'
  - Please score the impact of fatigue/low energy levels/tiredness on your overall QoL
  - Please score the impact of poor brain functioning (e.g., concentration or alertness) on your overall QoL *[item intended to measure cognitive impairment]*
  - Please score the impact of emotional/mental health on your overall QoL *[item intended to measure depression]*
  - Please score the impact of pain on your overall QoL
- Respondent's QoL was deemed to be impacted if they recorded a 4 or 5 on the Likert scale for the respective symptom question
- Respondents were grouped according to the number and type of co-occurring symptoms that had reportedly impacted their QoL

Semi-structured interviews and focus groups

- Interviews and focus groups were conducted with 25 MS patient experts to gather insights on the interconnected nature of symptoms, including fatigue, cognitive impairment, depression, and pain in PlwMS
- These were conducted by a patient expert who had been trained by the European Patients' Academy on Therapeutic Innovation (an organization that trains patients and patient representatives on the end to end process of medicines research and development), and accompanied by a market research expert moderator for support
- These qualitative data were analysed by reviewing recordings, capturing outcomes in a spreadsheet, and identifying core patient insights based on patterns in participant responses

Literature search

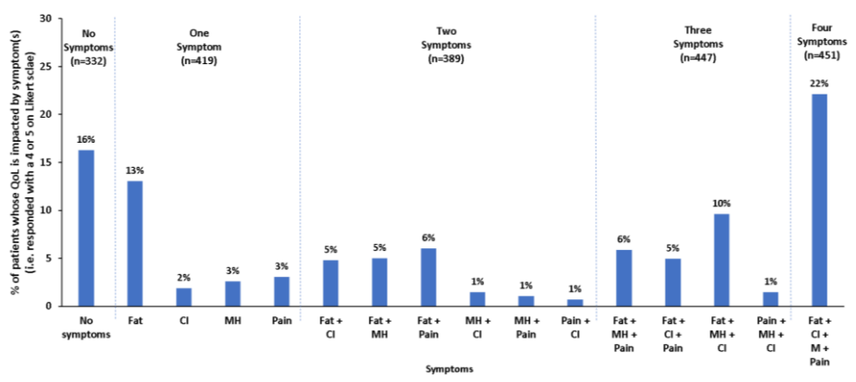
- A literature search aimed to identify published articles containing information on biological processes associated with the interconnectivity between fatigue, cognitive impairment, depression, and pain in PlwMS
- PubMed was searched across the last 10 years using the following terms: Multiple Sclerosis AND ((cognition AND fatigue AND depression) OR (cognition AND fatigue AND pain) OR (cognition AND pain AND depression) OR (fatigue AND pain AND depression)). 693 articles were returned in the search
- Non-relevant articles were discarded based on an initial assessment of titles (n=405), followed by a further removal of non-relevant articles based on abstract reviews (n=212)
- The remaining 76 articles were reviewed in full, and relevant information and themes were recorded

Results

Co-occurrence of symptoms impacting QoL

- Of the 2,052 patients who completed the LLY survey, 1,723 (84%) were female and 65%, 12%, 11%, and 1% had relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and clinically isolated syndrome, respectively. 11% did not know their MS type
- 16% of respondents reported that none of the symptoms (i.e. fatigue, cognitive impairment, depression, or pain) impacted their QoL, while 22% reported that all four symptoms of interest impacted their QoL. 63% reported the co-occurrence of symptoms (i.e. 2 or more symptoms) **(Figure 1)**
- Fatigue (13%) was the most commonly reported symptom to impact QoL among those who only reported being impacted by a single symptom, and was also the most commonly reported symptom among respondents impacted by two or three symptoms **(Figure 1)**

Figure 1. Co-occurrence of symptoms impacting QoL in PlwMS

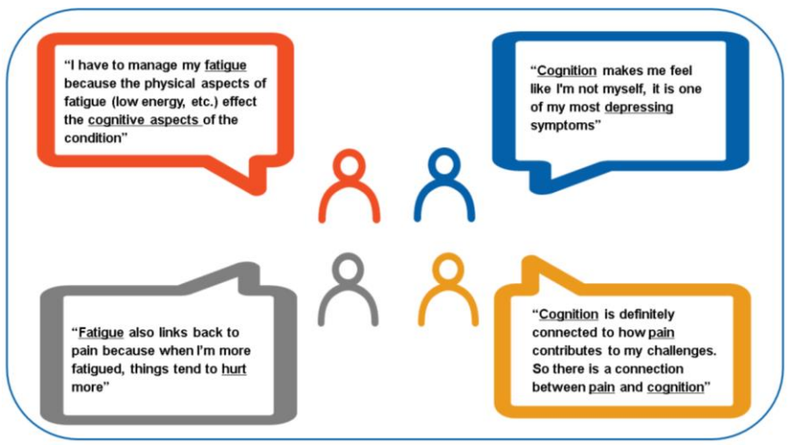


CI, cognitive impairment; Fat, fatigue; MH, mental health; PlwMS, people living with MS; QoL, quality of life. Data were missing for 14 participants for the questions related to symptom impact on QoL

Patient insights on symptom domain interconnectivity

- Of the 25 patient experts that took part in the interviews and focus groups, 18 (72%) were female, 16 (64%) were white, 24 (96%) had RRMS, and 1 had SPMS
- Key patient expert insights on symptom interconnectivity include:
- ***Fatigue***
  - Fatigue makes it difficult to manage emotions
- ***Cognitive impairment***
  - The memory of previous cognitive abilities and fear of future decline can bring on feelings of depression
- ***Depression***
  - Fatigue, pain, and cognitive impairment all contribute to feelings of depression
- ***Pain***
  - There is a clear relationship between fatigue and pain
- A selection of quotes from the patient experts are presented in **Figure 2** to demonstrate their experiences of how the four symptoms are interconnected

Figure 2. Patient expert quotes demonstrating symptom interconnectivity



Biological processes underpinning symptom interconnectivity

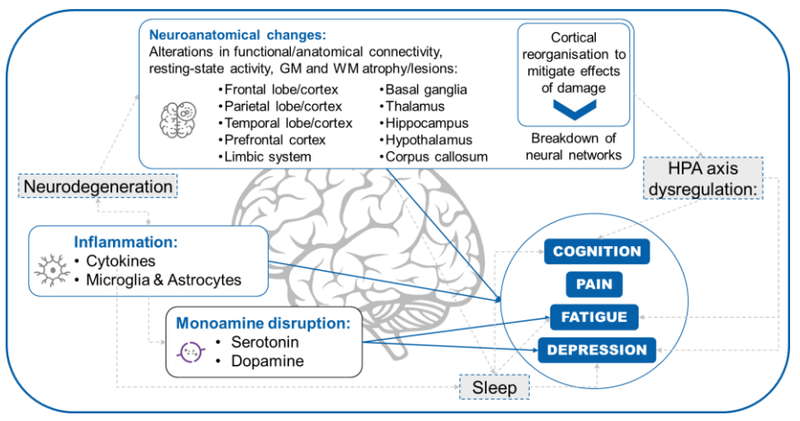
Literature search findings revealed three key mechanisms implicated in symptom interconnectivity (**Figure 3**):

1. **Neuroanatomical changes:** MS is associated with changes in structure, function, activity, and connectivity of a wide variety of brain regions. Resultant cortical reorganisation to mitigate effects of damage leads to the breakdown of neural networks
2. **Inflammation:** Cytokines and microglia play an important role in MS pathology. Changes in cytokines and T cells in blood and cerebrospinal fluid are associated with fatigue, cognitive impairment, depression, and pain. Microglia in lesions are associated with cognitive impairment, while microglia in the hippocampus are associated with depression. Microglia also play a pivotal role in the development of neuropathic pain
3. **Monoamine disruption:** MS-related neurodegeneration may affect regions involved in the synthesis and/or release of monoamines, and pro-inflammatory cytokines interfere with the synthesis, release, and uptake of serotonin and dopamine. Fatigue and depression in PlwMS have been associated with alterations in noradrenaline and serotonin transporters

These biological processes may also be mediated via sleep and the hypothalamic-pituitary-adrenal (HPA) axis (**Figure 3**):

- **Sleep**: Sleep disorders in PlwMS can be the consequence of CNS injury, and both melatonin and sleep are disrupted in PlwMS, which is associated with depression and fatigue
- **HPA axis**: This complex feedback loop is implicated in the control of the neuroendocrine system. Cytokines/inflammation can disrupt normal HPA axis functioning. Resultant altered hormone levels are associated with depression, fatigue, and cognitive impairment in PlwMS

Figure 3. Biological processes underpinning symptom interconnectivity



CNS, central nervous system; GM, grey matter; HPA, hypothalamic-pituitary-adrenal; WM, white matter

Discussion & Conclusions

- While recognizing the limitations of the methods used, our findings provide additional evidence for the co-occurrence of symptoms in PlwMS impacting QoL, as well as setting the groundwork for future investigations of unifying biological processes that might be driving symptom interconnectivity
  - In a large international sample of PlwMS, more than half of respondents reported the co-occurrence of symptoms that had an impact on their QoL
  - Qualitative information from interviews/focus groups further contextualized the nature of symptom interconnectivity
  - Literature search findings identified three potential biological processes driving these relationships between symptoms
- While this preliminary investigation into symptom interconnectivity provides a starting point for future work, much research is required before definitive answers can be found regarding the biological underpinnings, including:
  - Studying sub-groups of PlwMS who experience some, none, or all of the symptoms in question, to identify biological differences between these groups
  - Ensuring that existing PROs are designed, validated, and fit for purpose to assess the symptoms in question
  - Ensuring that independent symptom domains (e.g. fatigue) and biological outcomes are collected in future studies to allow for robust investigation into the associations between these variables
  - Developing new PROs where gaps exist, that are based on well-defined conceptual frameworks

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